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Article

Study of the Inversion Reaction of the Lactonic Fusion on Eremanthine Derivatives

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As α-metileno-γ-lactonas 4(15)-diidroeremantina (**8**), 4(15),9(10)-tetraidroeremantina (**9**), isoeremantina (**10**), acetato alílico $\Delta^{1,10}$ (**11**), 1(R),10(R)-diidromiqueliolido (**12**) e 4α-hidróxi acetato alílico $\Delta^{1,10}$ (**13**) foram sintetizadas a partir do produto natural abundante eremantina (**1**). Essas substâncias foram submetidas à reação de hidrólise com KOH aquoso e os sais carboxílicos dessas lactonas tiveram suas hidroxilas ativadas na posição C-6, pela formação dos respectivos mesilatos (MsCl, Et_3N, THF ou DMSO) para deslocamento nucleofílico efetuado pelo grupo carboxilato. A utilidade dessa metodologia foi investigada para a obtenção de guaianolidos com fusão lactônica *cis* na posição C6-C7 e para sintetizar um precursor para estudo posterior da transformação biomimética de guaianolidos em pseudoguaianolidos.

The α-methylene-γ-lactones 4(15)-dihydroeremanthine (**8**), 4(15),9(10)-tetrahydroeremanthine (**9**), isoeremanthine (**10**), allylic acetate $\Delta^{1,10}$ (**11**), 1(R),10(R)-dihydromicheliolide (**12**) and 4α-hydroxy allylic acetate $\Delta^{1,10}$ (**13**) were synthesized from the abundant natural product eremanthine (**1**). These substances were submitted to hydrolysis reaction with aqueous KOH and the carboxylic salts of these lactones had their hydroxy groups activated at the C-6 position by formation of respective mesylates (MsCl, Et_3N, THF or DMSO) which underwent further displacement by carboxylate group. The utility of this methodology was investigated in order to obtain guaianolides with *cis* lactonic fusion at the C6-C7 position and to synthesize a precursor for posterior study of the biomimetic transformation of guaianolides into pseudoguaianolides.

Keywords: eremanthine, inversion of configuration, molecular conformation

Introduction

Sesquiterpene lactones, with their several skeletons, constitute a great class of natural products generally found in *Compositae* family. Among these sesquiterpenolides, two groups of substances have received considerable attention in what refers to isolation and synthesis, due to their biological properties and varied structural patterns. These substances are the guaianolides and their biogenetical derivatives, the pseudoguaianolides.[1]

Guaianolides have the skeleton of bicyclo[5.3.0]decane, characteristic of sesquiterpenes denominated guaianes, to which was inserted at positions C-6 and C-7 or C-7 and C-8 a γ-lactonic ring containing in C-11 a methyl group or a vinylic methylene and at positions C-4 and C-10 methyl groups or vinylic methylenes. As examples of guaianolides we can cite eremanthine (**1**), a schistosomicidal substance isolated from Brazilian compositae *Eremanthus elaeagnus* and *Vanillosmopsis erythropappa*,[2] and gaillardin (**2**)[3] (Figure 1).

Pseudoguaianolides also have the skeleton of bicyclo[5.3.0]decane to which is associated a γ-lactonic ring. They usually have a β-methyl group at C-5 position and are classified as ambrosanolides and helenanolides according to the stereochemistry of methyl group at C-10; in other words, ambrosanolides have β-methyl and helenanolides an α-methyl in this position. Damsin (**3**)[4] and carpesiolin (**4**)[5] are ambrosanolides and helenalin (**5**)[6] and aromatin (**6**)[7] are helenanolides examples (Figure 2).

Continuing the research program about chemical transformations of eremanthine (**1**), whose initial results were published in a recent article,[8] in this paper we report the syntheses of 4(15)-dihydroeremanthine (**8**), 4(15),9(10)-tetrahydroeremanthine (**9**), isoeremanthine (**10**), allylic acetate $\Delta^{1,10}$ (**11**), 1(R),10(R)-dihydromicheliolide (**12**) and 4α-hydroxy allylic acetate $\Delta^{1,10}$ (**13**) and posterior reaction of lactonic fusion inversion on these derivatives (Figure 3). It was evaluated in this study of lactonic inversion on

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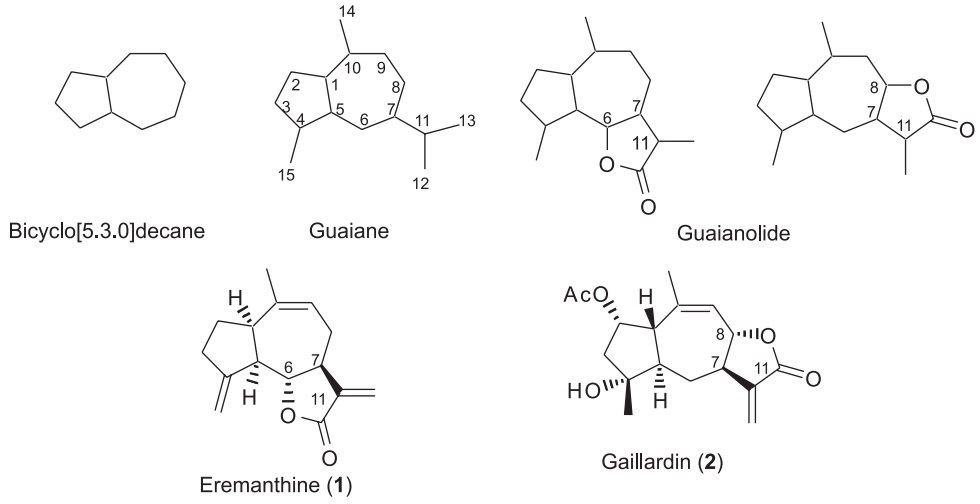


Figure 1. Guaianolides.

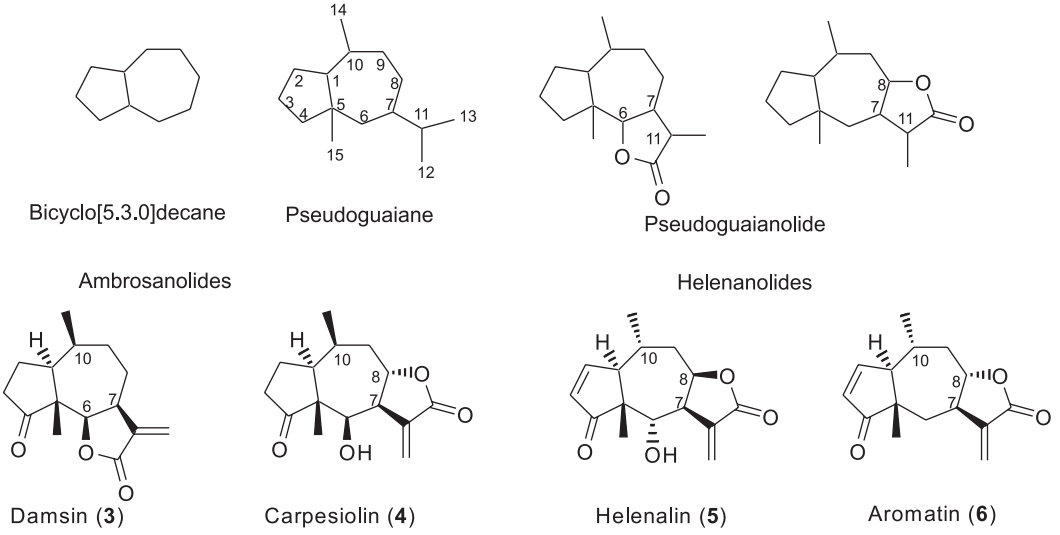


Figure 2. Pseudoguaianolides.

eremanthine derivatives, the viability of obtaining guaianolides with *cis* lactonic fusion at the C6-C7 position and substances containing the structural requirements for subsequent study of biomimetic transformation of guaianolides into pseudoguaianolides.

Strategies for the syntheses of eremanthine derivatives

Previous studies on the lactonic fusion inversion of eremanthine (**1**) led to the synthesis of 6-*epi*-eremanthine (**7**) (see Figure 3) that was shown unstable. Such instability was attributed to conformational effects of hydroazulene system[9] that resulted in a high tension at the lactonic ring, evidenced through its infrared spectral data.[10,11] Due to the instability of synthesized 6-*epi*-eremanthine, it was intended to evaluate the reactivity of eremanthine derivatives in the reaction of lactonic fusion inversion, in order to obtain more stable epimers.

For this study of stereochemical inversion on the C-6 position, it was idealized to synthesize substances derived from **1** differing in the unsaturation degree as well as in the positions of double bonds at the hydroazulene system. Such procedure would result in the formation of substances, that we denominated as models, with different conformations and steric interactions among their functional groups, due to the flexibility of the system in study. Therefore, the models **8-13** (Figure 3) were selected to be submitted to conditions of lactonic fusion inversion.

The synthesis of substance **8** was idealized through the chemoselective reduction of double bond C4-C15 at the eremanthine methoxy derivative (**14**), with hydrogen and catalyst, followed by restoration of α-methylene-γ-

lactone for methanol elimination.[12] The synthesis of substance **9** was planned in the same conditions employed in the conversion of **14** in **8** using, in this case, more drastic conditions of hydrogen pressure during the stage of catalytic hydrogenation, since trisubstituted double bond (C9-C10) is less reactive than disubstituted double bond (C4-C15). Isoeremanthine (**10**) was previously synthesized from isomerization of double bond C4-C15 of eremanthine (**1**) to C3-C4 position and it would be obtained by the same procedure.[13] For the synthesis of allylic acetate **11** we planned to obtain it through an elimination step of iodohydrins **18-19**, previously described,[14] by metal in acid medium to generate the respective products **16** and **11**.[15] In the case of allylic alcohol **16**, it would be made an additional stage of protection at the hydroxy group in C-9 position through an acetylation reaction for obtention of compound **11**. Alternatively, substance **11** would be obtained starting from iodohydrin **20**,[8] by the same procedure used in the conversion of **18** in **16**, followed by stage of methanol elimination commonly used with eremanthine derivatives[12] and subsequent acetylation of hydroxy group at C-9 position. Substance **12**, previously synthesized from diol **21**,[8] would be obtained by the same procedures. Substance **13** would be obtained by simple reaction of methanol elimination accomplished on compound **21**, previously described,[8] followed by acetylation of hydroxy group at C-9 position.

Results and Discussion

The syntheses of models **8-13** were performed according to conditions described in Scheme 1.

Initially, eremanthine methoxy derivative (**14**), obtained from previously described procedure,[8] was submitted to hydrogenation reaction catalyzed by palladium on charcoal using a hydrogen pressure of 40 psi at the conditions **i** described in Scheme 1. After the time of reaction, a product was isolated and then submitted to ^{1}H NMR. The spectrum indicated that we obtained a mixture of epimers at C-4 position, in the proportion of 1:1, due to the presence of singlets with same intensity at δ 3.34 and 3.33 ppm relative to hydrogens of methoxy groups, as well as the doublets of methyl groups C15-H at δ 1.13 (J 6.6 Hz) and 0.94 (J 6.2 Hz). In the step **ii**, we submitted the mixture of intermediate epimers, resultant of hydrogenation of **14**, to stage of methanol elimination for restoration of α-methylene-γ-lactone. Crude product was purified by column chromatography to give a 1:1 mixture of epimers **8a** and **8b**, identified by ^{1}H NMR.

For the synthesis of model **9** it was used the conditions **iii-iv** described in Scheme 1. The crude product obtained in these two steps was purified by column chromatography and then submitted to ^{1}H NMR. The spectrum revealed that we obtained a mixture of 3 substances in a proportion of 2:5:3, measured by

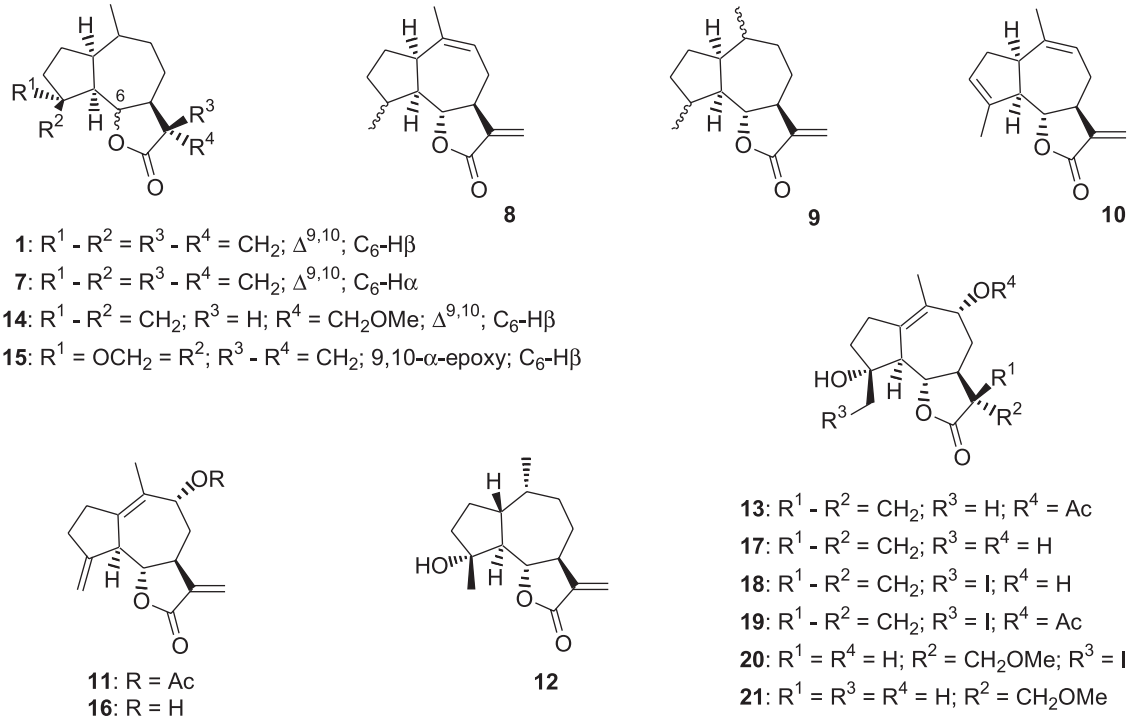
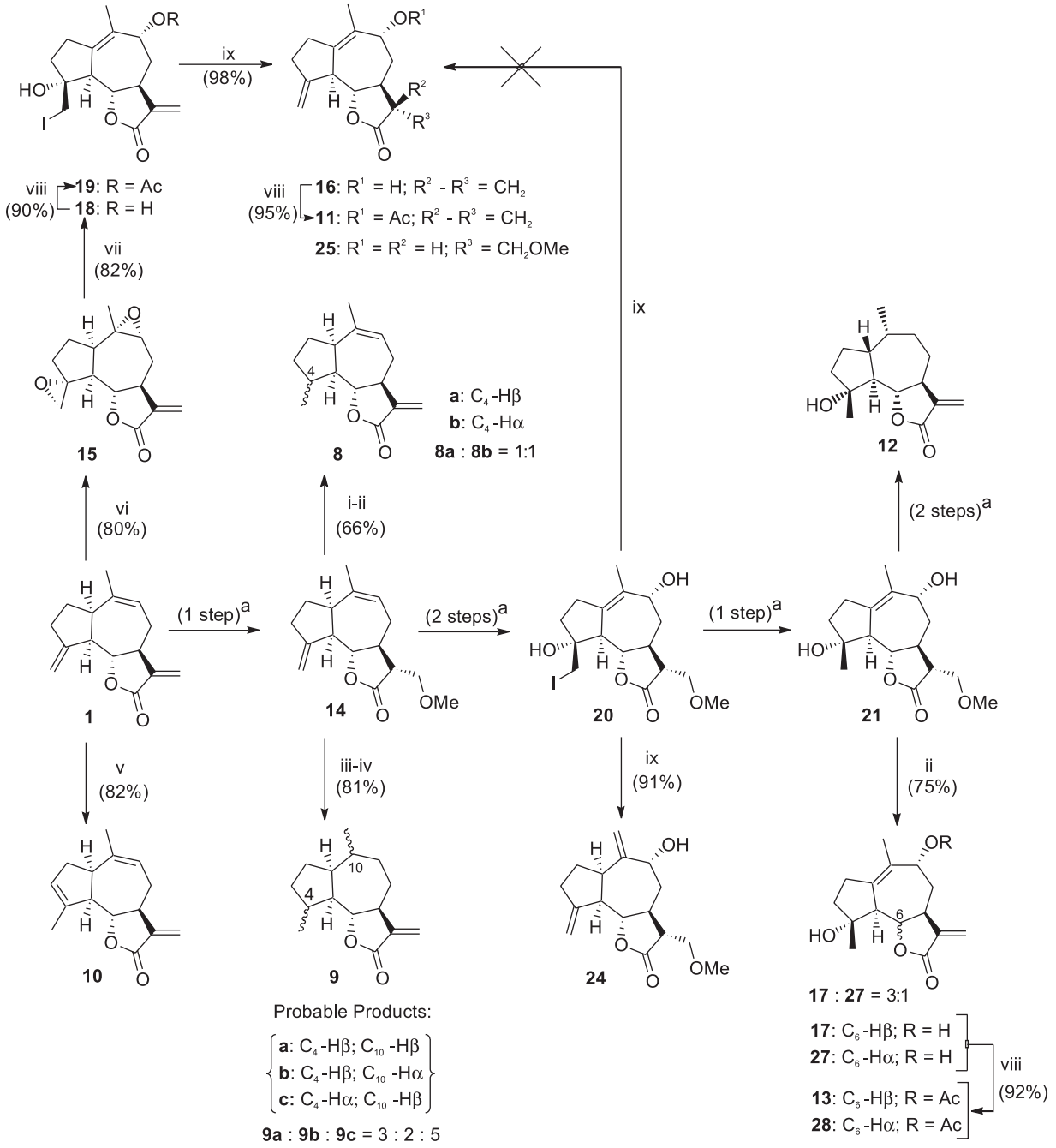
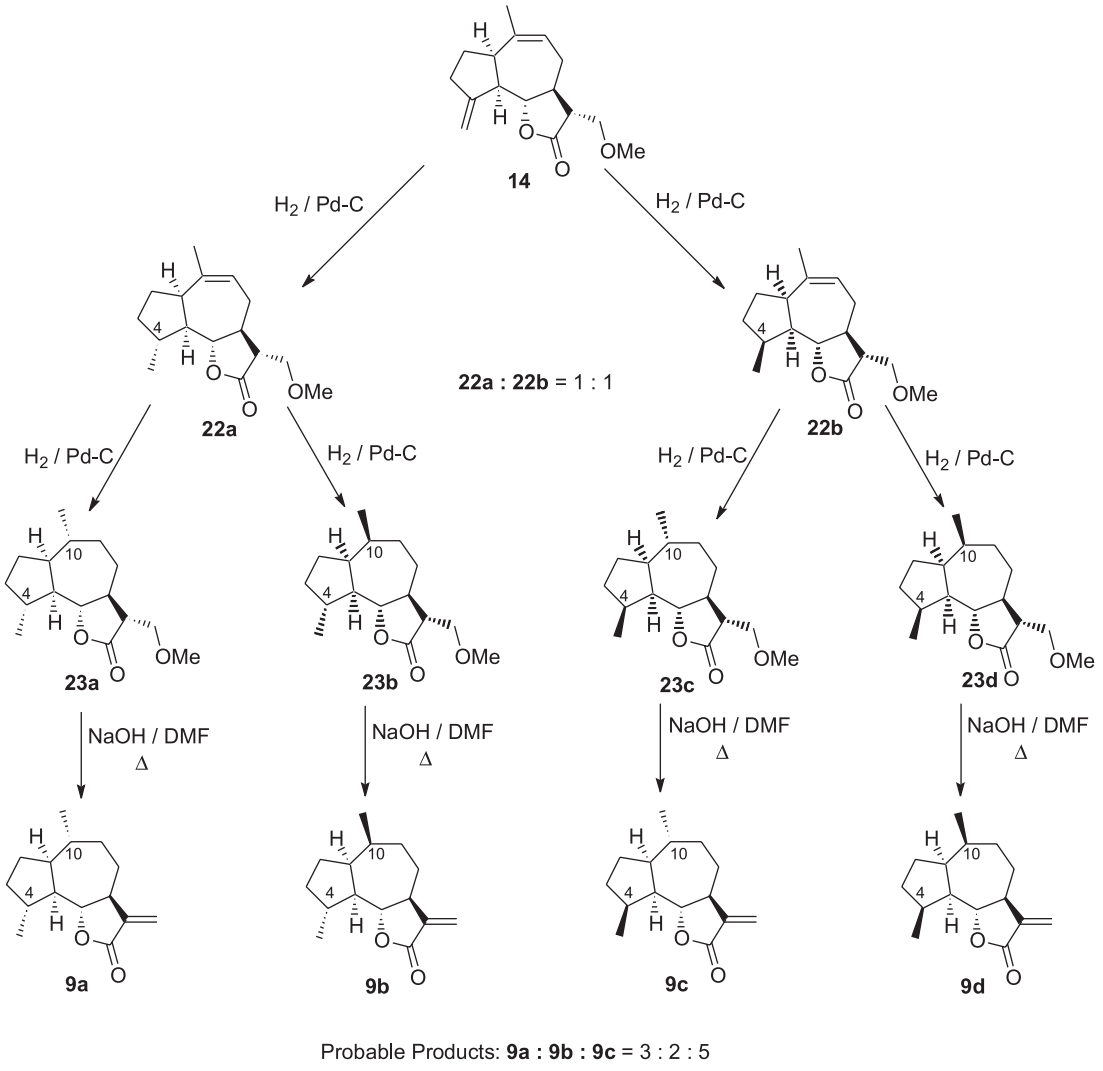


Figure 3. Eremanthine (**1**) and synthetic derivatives.



Scheme 1. Reagents and conditions: *i*) H_2 (40 psi), 10% Pd-C (0.05 equiv.), EtOH (r. t. - 1 h); *ii*) 4 mol L^{-1} NaOH (5.5 equiv.), DMF (reflux - 2 h); *iii*) H_2 (60 psi), 10% Pd-C (0.1 equiv.), EtOH (r. t. - 4 h); *iv*) 4 mol L^{-1} NaOH (5.5 equiv.), DMF (reflux - 6 h); *v*) $BF_3.OEt_2$ (1.1 equiv.), benzene (r. t. - 5.5 h); *vi*) AcO_2H / $CHCl_3$ (r. t. - 96 h); *vii*) KI (1.1 equiv.), AcOH (15 equiv.), acetone (reflux - 5 h); *viii*) Ac_2O / pyridine (r. t. - 2 h); *ix*) Zn (15 equiv.), AcOH (5 equiv.), EtOH (reflux - 30 min.). [a] See reference 8.

respective integrals relative to the signals of hydrogens C6-H at δ 4.17 (t, *J* 10.5 Hz), 4.02 (dd, *J* 9.3 and 10.2 Hz) and 3.81 (t, *J* 9.9 Hz). The probable products obtained in these reactions are shown in Scheme 2. As we had observed before in the chemoselective hydrogenation stage of double bond C4-C15 on the eremanthine methoxy derivative (**14**), it was obtained a 1:1 mixture identified by ^{1}H NMR as epimers **22a** and **22b** (Scheme 2). When this mixture, generated *in situ*, is submitted to subsequent stage of catalytic hydrogenation for reduction of trisubstituted double bond C9-C10, we expect to obtain the 4 diastereoisomers (**23a-d**) shown in Scheme 2. However, it was observed at the ^{1}H NMR spectrum of final product, after stage of methanol elimination, the signals relative to a mixture of only 3 substances. From the calculations of steric



Scheme 2. Diastereoisomers of model **9**.

energies (Table 1), by using MM2 program,[16] for the probable products (**23a**-**d**) obtained after stage of catalytic hydrogenation, we can deduce that the products of this reaction in crescent order of steric energy are the substances **23a**-**c**, that submitted to subsequent stage of methanol elimination give as final products the respective diastereoisomers **9a**-**c**. According to proportion of the three products verified at the ^{1}H NMR spectrum, we can do the following suppositions: as the substances **22a** and **22b** are generated in same amounts and being considered that formation of compound **23d** is disfavored due to steric effects of two bulky methyl groups both in axial β-position (C14-H and C15-H), we can conclude that compound **22b** just generates a diastereoisomer, the compound **23c** (50% of the mixture). Compound **22a**, for its time, will be responsible for the formation of the other 50% of the mixture. In this case as product **23a**, with the bulky methyl groups C14-H and C15-H in equatorial α-position, presents less steric interactions than product **23b** that has the bulky methyl group C14-H in axial β-position and C15-H in equatorial α-position, we can expect that **23a** are in a larger proportion in the mixture than compound **23b** (30% versus 20%). These substances when are submitted to stage of methanol elimination give their respective α-methylene-γ-lactones **9c**, **9a** and **9b** in a respective proportion of 5:3:2.

For the synthesis of model **10**, previously described,[13] we used conditions **v** (Scheme 1). After the time of

Table 1. Steric energies for diastereoisomers **23a-d**

Substances	Steric Energies (kcal mol^{-1})
23a	39.144
23b	39.404
23c	40.289
23d	40.970

reaction, a product was isolated and then identified as isoeremanthine (**10**) by spectroscopy methods. This substance was obtained with high purity, evidenced at the TLC and at their NMR spectra not needing, therefore, of additional purification.

For the synthesis of model **11**, previously described,[15] we employed conditions **vi-ix** as outlined in Scheme 1. Epoxidation of eremanthine (**1**) with diluted solution of peracetic acid in chloroform, in conditions **vi**, generated a product identified as diepoxide **15**. This substance was previously obtained in the same conditions described in Scheme 1 using dichloromethane as the solvent of reaction.[17] Opening of oxiranic rings of crude product **15**, in acid medium, with equimolar amount of KI and reflux of acetone (step **vii**) generated a product that was purified by column cromatography and then identified as iodohydrin **18**. Acetylation of substance **18** at the conditions **viii** yielded acetate **19**. When the substances **18** and **19** were submitted to elimination conditions by metal in acid medium (step **ix**) it was obtained the respective trienes **16** and **11** in almost quantitative yield. These substances were obtained with high purity evidenced at the TLC and at their NMR spectra no needing, therefore, of additional purification. Soon afterwards the hydroxy group at C-9 position of compound **16** was protected to give allylic acetate **11** (step **viii**). This protection stage of allylic alcohol **16** was accomplished in order to avoid elimination reaction when exposed to $MsCl/Et_3N$ during step of lactonic inversion, since previous attempts of obtaining the mesylate at C-9 position derived from allylic alcohol **20**, gave elimination products with formation of conjugate dienes.[18] When this same elimination reaction by metal in acid medium (step **ix**) was accomplished on iodohydrin **20**, for our surprise we obtained substance **24** instead of the expected product **25**. After analysis of three-dimensional structures of the molecules involved in these processes of chemical transformations, by using MM2 program,[16] we verified that substances **25** and **16** have different conformations at the hydroazulene system (Scheme 3).

Cycloheptene ring, that commands the geometry of hydroazulene system, is in the chair form at substance **16**, with a plane of symmetry passing through the C-7 position (C_7) while substance **25** has the seven-membered ring in twist-boat conformation with a pseudo-C_2 axis passing through the C-8 position (TB_8).[9] Conformations of the seven-membered ring of substances **16** and **25**, obtained in the MM2 program[16] are shown at the Figure 4.

Starting from these observations, we concluded that substance **25** is initially generated as expected and then it should react with zinc species (I-Zn-OH)[11] obtained as subproducts of iodohydrin elimination, to give allylic alcohol **24**. In the case of allylic alcohol **16**, the subsequent isomerization reaction of double bond C1-C10 to C10-C14 position, catalysed by I-Zn-OH, should not occurs due to probable steric effects of conformation at this molecule that do not favor complexation of I-Zn-OH with the oxygen of hydroxy group at C-9 position and C-10 sp^2 carbon which concentrates a high electronic density. The free-radical mechanism depicted in Scheme 4 was proposed to reaction of reactive intermediate **25** with I-Zn-OH. In this case, the stereochemistry at C-1 position would be defined by stability of the final product, in other words, the radical **B** would react with the radical **H**· to generate the more stable isomer (**24**). This kind of zinc species complexation, between two sterically related functional groups, was previously proposed to reactions of iodohydrin **18** with zinc in acid medium and methanol as the solvent, in the generation of $O^{6,15}$-cycloguaianes derived from eremanthine.[11,14] The structure of substance **24** was confirmed by comparison of its ^1H NMR, IR and R_f data with the ones of this substance, previously obtained by opening of epoxide 9,10-α-epoxy-eremanthine in acid medium, followed by a protection stage of α-methylene-γ-lactone with methanol and sodium carbonate.[17] Moreover, analysing three-dimensional structures of compounds **24** and (**24**)-1-*epi*, obtained by MM2 program,[16] we can verify differences at these isomers that would implicate in different values of chemical shifts at the signals of

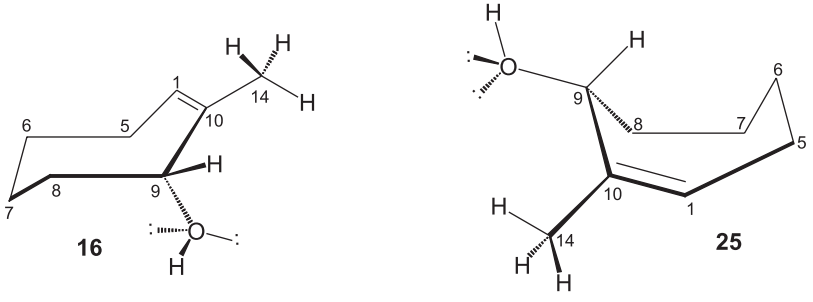
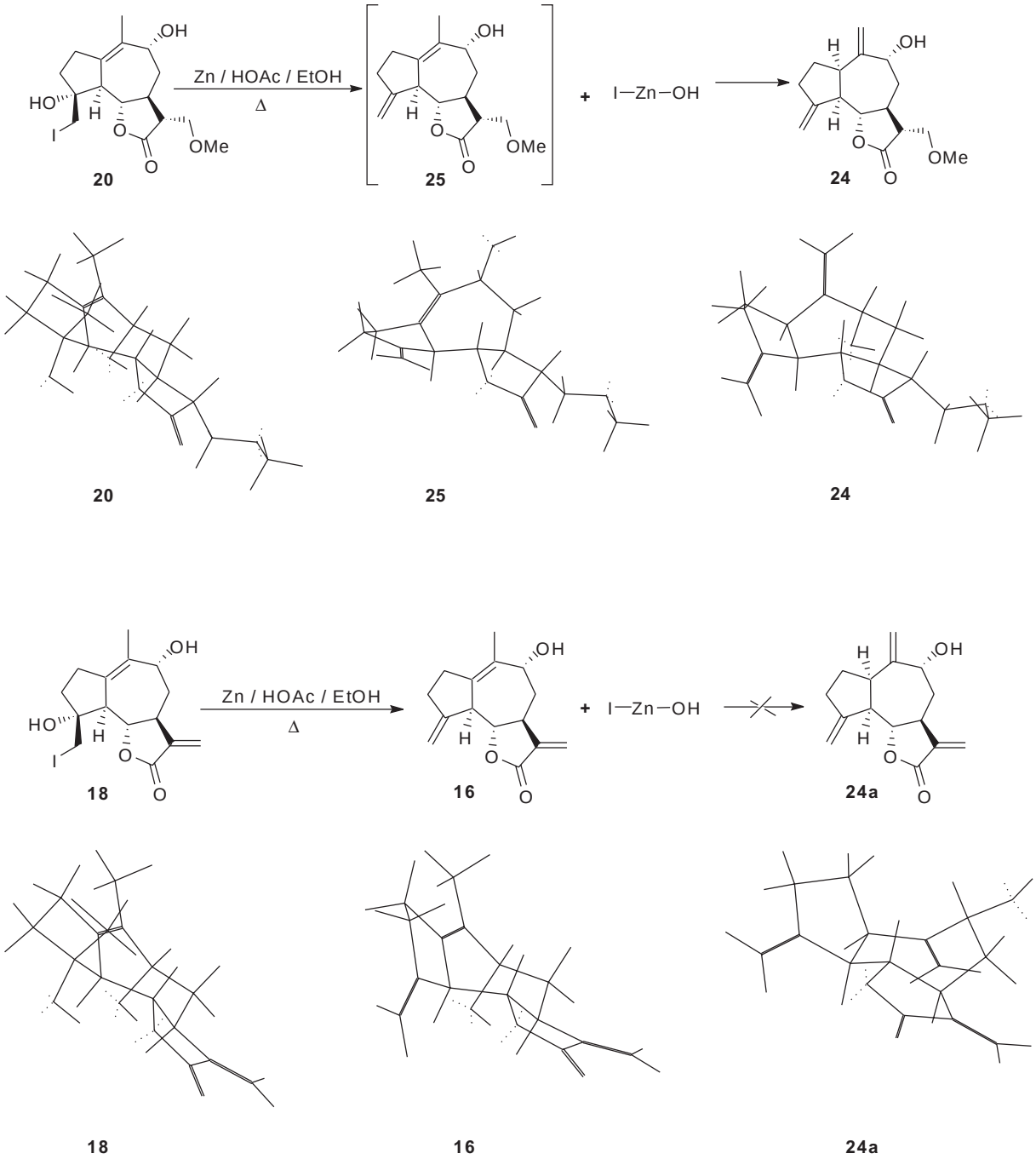


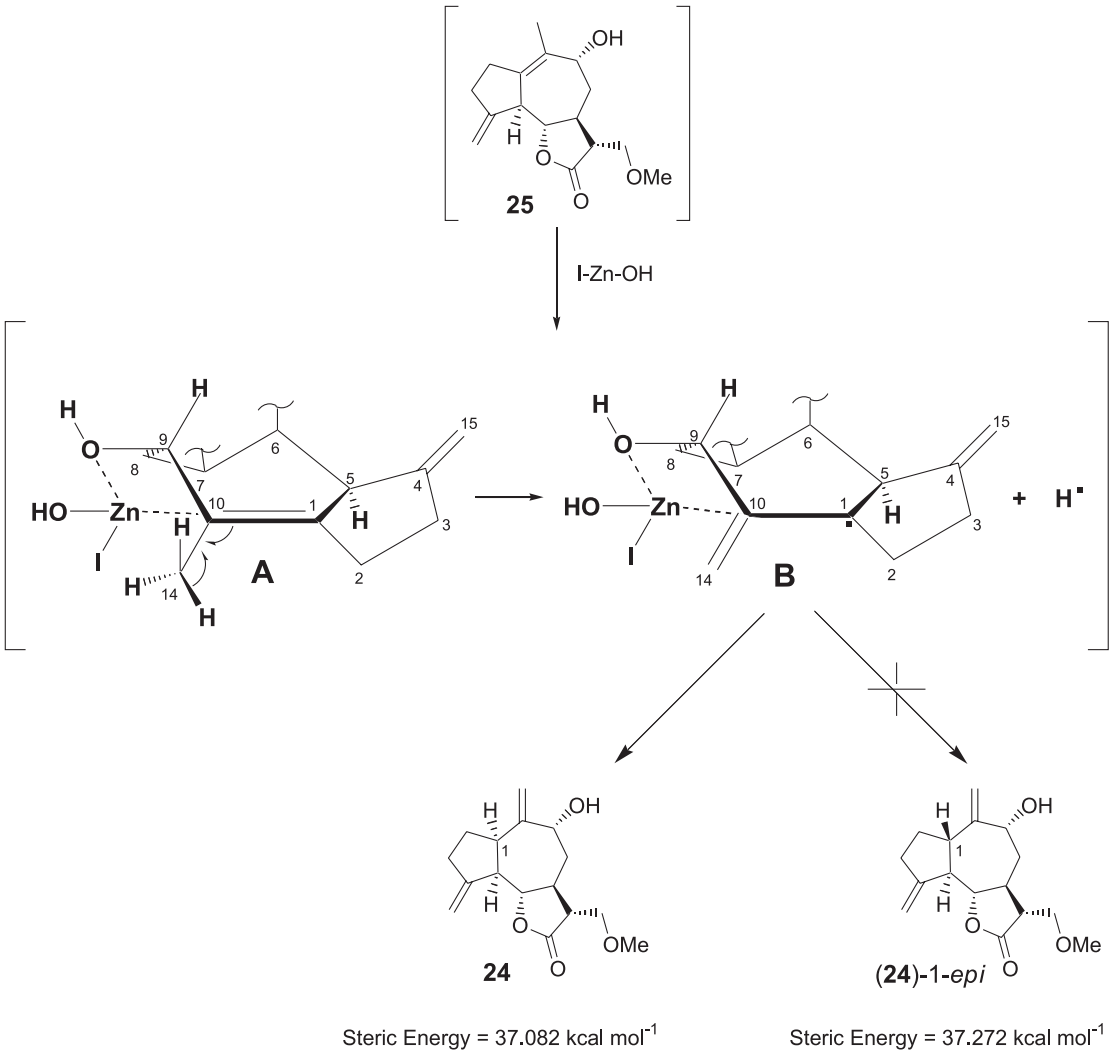
Figure 4. Conformations of the seven-membered ring for the substances **16** and **25**.



Scheme 3. Reactions of iodohydrins **20** and **18** with zinc.

hydrogens of two substances, mainly at the signal of C6-H (see Figure 5). At the isomer **24** this hydrogen is located at shielding area of double bond C10-C14 located in β-position. In the isomer (**24**)-1-*epi* this shielding effect should be attenuated, due to the change of conformation that puts double bond C10-C14 in α-position, opposed to hydrogen C6-H. These additional data of molecular modeling contributed to confirm the stereochemistry at C-1 position of substance **24**, since we had obtained the isomer (**24**)-1-*epi* its ^{1}H NMR data would be substantially different from those in reference 17.

The initial formation of reactive intermediate **25** in the generation of product **24**, described in Scheme 3, was confirmed in an experiment in which the reaction depicted in Scheme 1 (step **ix**) was interrupted after 10 minutes from its beginning. The TLC of crude product obtained in this reaction revealed the presence of two substances, with practically identical R_f. This mixture was submitted to ^{1}H



Scheme 4. Speculative mechanism for generation of allylic alcohol **24**.

NMR and it was detected in its spectrum the presence of signals attributed to intermediate **25** and product **24** in a respective proportion of 7:4, measured by integrals relative to C9-H signals at δ 4.23 (bd, *J* 5.5 Hz; C9-H of **25**) and 4.48 (t, *J* 3.5 Hz; C9-H of **24**). Signals of the main hydrogens attributed to intermediate **25** in this spectrum are shown in Table 2.

The synthesis of substance **12** was described in a recent article about chemical transformations of eremanthine (**1**).[8] When diol **21** was submitted to step **ii** of methanol elimination depicted in Scheme 1, it was obtained a mixture of two products with practically identical R_f in a proportion of 3:1, measured by integrals relative to the signals of C13-H of the two products at ^{1}H NMR spectrum. Major product corresponded to diol **17** previously described[11] and minor product was later characterized as epimer **27**, for occasion of the lactonic inversion reaction of substance **17** protected in the form of its allylic acetate **13**, by comparison of ^{1}H NMR spectra obtained by the two procedures. Soon afterwards the mixture of epimers **17** and **27** was submitted to protection stage **viii** (Scheme 1) of hydroxy groups at C-9 position. The major product of this reaction was separated by column chromatography and then identified as allylic acetate **13** for spectroscopy

Table 2. Selected chemical shifts for the hydrogens of intermediate **25** (^{1}H NMR)

Hydrogens	δ (Multiplicity, *J* / Hz)[a]
H_a-15	5.11 (bs)
H_b-15	5.03 (bs)
H-9	4.23 (bd, 5.5)
H-6	3.68 (m)
H-13	3.64 (m)
H-16	3.33 (s)
H-14	1.79 (bs)

[a] Assignment for the hydrogens of intermediate **25** was made by comparison with those of allylic alcohol **16**.

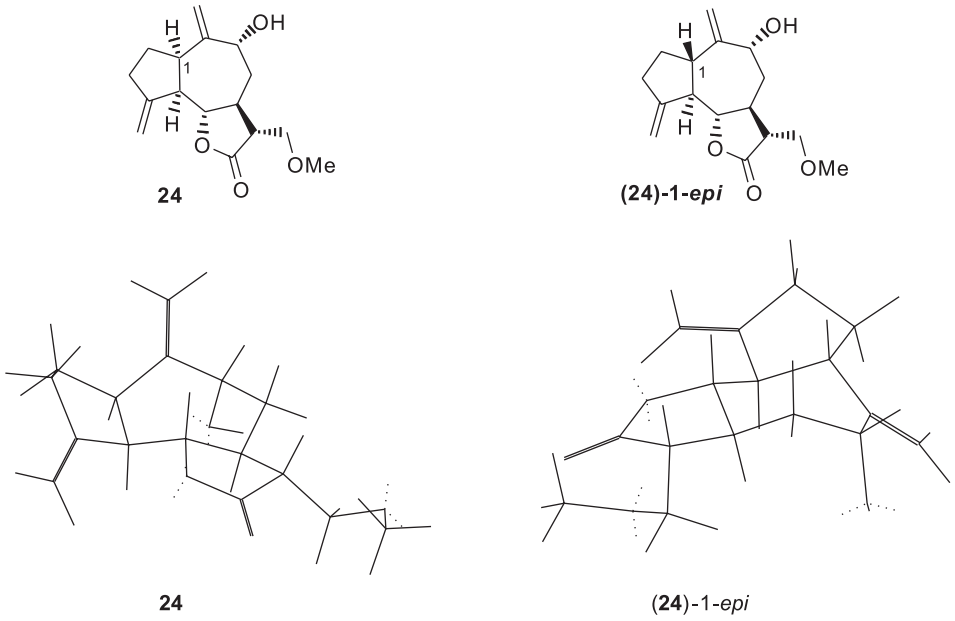


Figure 5. Comparison of the three-dimensional structures of epimers **24** and (**24**)-1-*epi*.

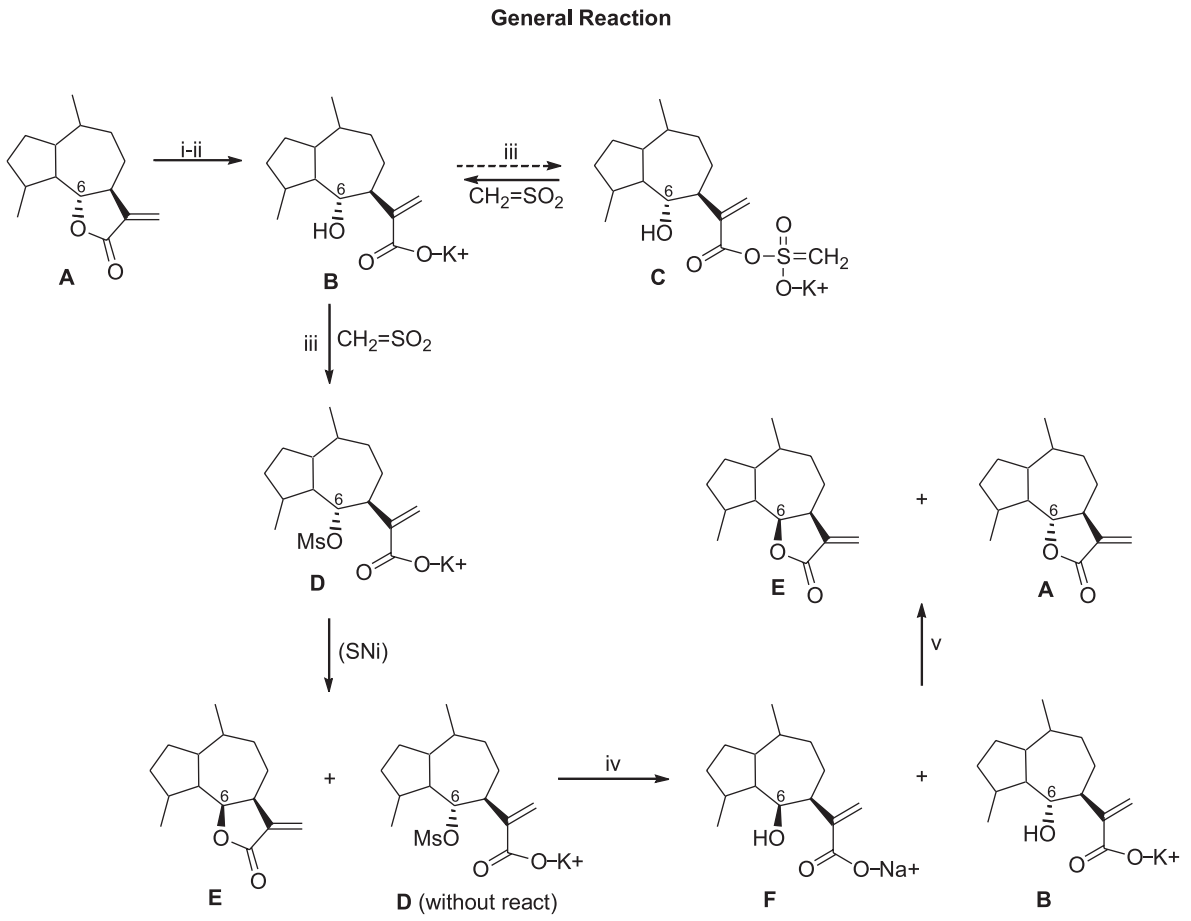
methods. This epimeric mixture, obtained at the stage of methanol elimination, was only verified with substance **21** containing double bond at the C1-C10 position of hydroazulene system. This facility to generate product with inversion of configuration at the C-6 position of diol **17** was verified for occasion of the study of lactonic fusion inversion on eremanthine derivatives.

After the preparation of models **8-13** we started the study of the lactonic fusion inversion on these compounds.

Reactions of the lactonic fusion inversion on eremanthine derivatives

The study of the transformation of eremanthine derivatives with *trans* lactonic fusion into substances with *cis* lactonic fusion was accomplished by stereochemical inversion on the alkoxy carbon of the lactonic ring. There are three classic methods to make the configuration inversion on secondary hydroxy groups: the first of them is the traditional method of oxidation-reduction,[19] in which a hydroxy group is oxidized in a first stage to a ketonic carbonyl group, for in the following stage to be stereoselectively reduced by hydride, to give in the end a hydroxy group with opposite stereochemistry to that of initial secondary alcohol. The inversion of configuration of secondary hydroxy groups can also be made through Mitsunobu's reaction,[20] in which occurs the activation of hydroxy group in a first stage by formation of an alkoxyphosphonium, for soon afterwards to occur the nucleophylic displacement of this activated leaving group. In the last case, we can cite the method of hydroxy activation by formation of correspondent mesylate, in which the inversion of configuration occurs by nucleophylic displacement of mesylate leaving group.[21] For the study of stereochemical inversion on alkoxy carbon of the lactones derived from eremanthine (**1**), we opted for the use of intramolecular displacement of mesylate, since this reaction was previously well described during the stereochemical inversion on the alkoxy carbon of a γ-lactone with hydroazulene skeleton[22] and during the synthesis of 6-*epi*-eremanthine.[10,11] Attempts to make inversion of configuration on alkoxy carbon of a γ-lactone with hydroazulene skeleton by displacement of alkoxyphosphonium[22] or by oxidation-reduction on C6-OH of an eremanthine derivative[10,11] were unsuccessful.

To study the lactonic fusion inversion on eremanthine derivatives, we used the reaction conditions outlined at Scheme 5 and previously described for the synthesis of 6-*epi*-eremanthine.[10,11] Therefore, the models **8-13** were submitted to reaction conditions depicted in Scheme 5, in which at the stage **i** starting materials (**A**) were treated with aqueous solution of potassium hydroxide to generate the correspondent carboxylates (**B**). At stage **ii**, we proceeded to evaporation of water and then dryness of residual product in high vacuum. At stage **iii** dried carboxylates (**B**) were submitted to treatment with trietylamine and mesyl chloride, conditions wherein sulfene is generated. This reactive species should react with carboxylates in a reversible way to give intermediates such as **C**, while the reaction of sulfene with the hydroxy group at C-6 should be unreversible to generate intermediates as **D**.[22] Soon

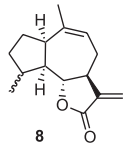
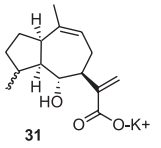
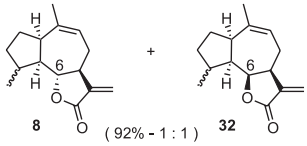
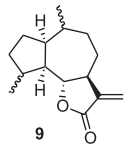
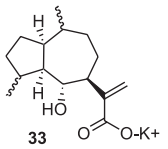
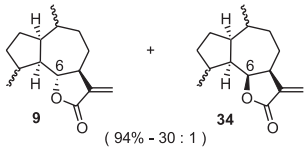
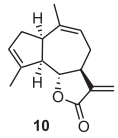
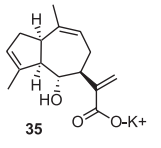
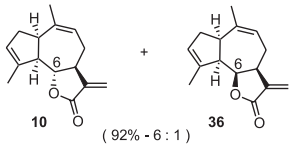
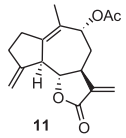
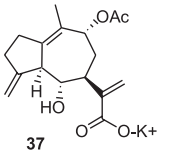
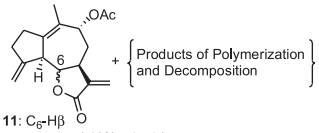
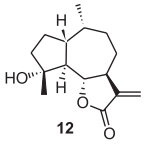
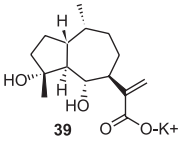
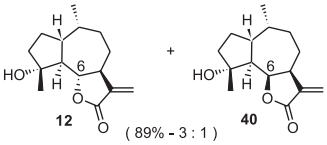
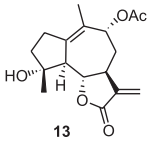
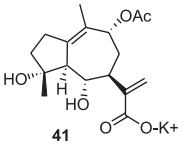
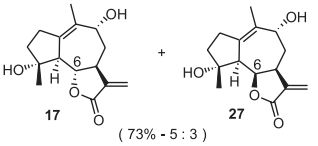
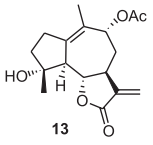
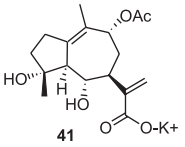
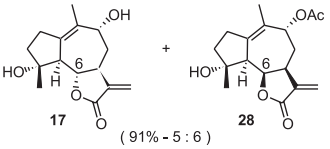


Scheme 5. Reagents and conditions: *i*) Aqueous 4% KOH (4.6 equiv.);[a] *ii*) dryness; *iii*) MsCl (6.0 equiv.), Et_3N (7.0 equiv.), Solvent (THF or DMSO) (0 °C - 1 h; r. t. - 3 h); *iv*) 0.2 mol L^{-1} NaOH (3.2 equiv.; 50 °C - 1 h); *v*) 10% (v/v) HCl, pH 3. [a]Time and temperature of hydrolysis reactions are indicated in Table 3.

afterwards, the intramolecular nucleophilic substitution (SNi) should occurs at the intermediates **D** to give the compounds **E** with *cis* lactonic fusion, along with any mesylates **D** that did not react. At stage **iv** it was used aqueous solution of sodium hydroxide to hydrolize any mixed anhydrides (**C**) as well as the mesylates at C-6 (**D**) that did not suffer nucleophilic displacement by carboxylates. At stage **v** aqueous solution of hydrochloric acid was added until pH 3 to convert the carboxylates into respective hydroxy-acids in order to lactonize them giving, in the end, epimeric mixtures at C-6 (**A** + **E**). Crude products of the reactions depicted at Scheme 5 were extracted with organic solvent and then submitted to ^{1}H NMR. The proportion of epimeric products obtained in these reactions was measured by the integrals relative to the signals of C13-H. A common characteristic observed at ^{1}H NMR spectra of products with *cis* lactonic fusion is related to position of the signals relative to these hydrogens. It was verified at spectra of epimeric mixtures of models **8-13** that all products with *cis* lactonic fusion presented the signals of C13-H located in higher values of chemical shifts in relation to the ones of substances with *trans* lactonic fusion. In the cases in which starting materials, with *trans* lactonic fusion, had double bond at C1-C10 or C9-C10 positions, a deshielding effect was verified at the hydrogen C6-H of their epimers evidenced at the respective ^{1}H NMR spectra. This deshielding effect observed at the C6-H signals of products with *cis* lactonic fusion was attributed to position change of these hydrogens that passed from the axial position at products with *trans* lactonic fusion (located at shielding area, on the electronic cloud of double bonds C1-C10 or C9-C10) to equatorial position, no more on the respective electronic clouds. The *cis* fusion at the products of lactonic inversion was verified by equatorial-equatorial coupling constants at the C6-H signals. Products of lactonic fusion inversion of models **8**-**13** are depicted in Table 3 and chemical shifts of the main hydrogens at starting materials and products of inversion reactions are in Table 4.

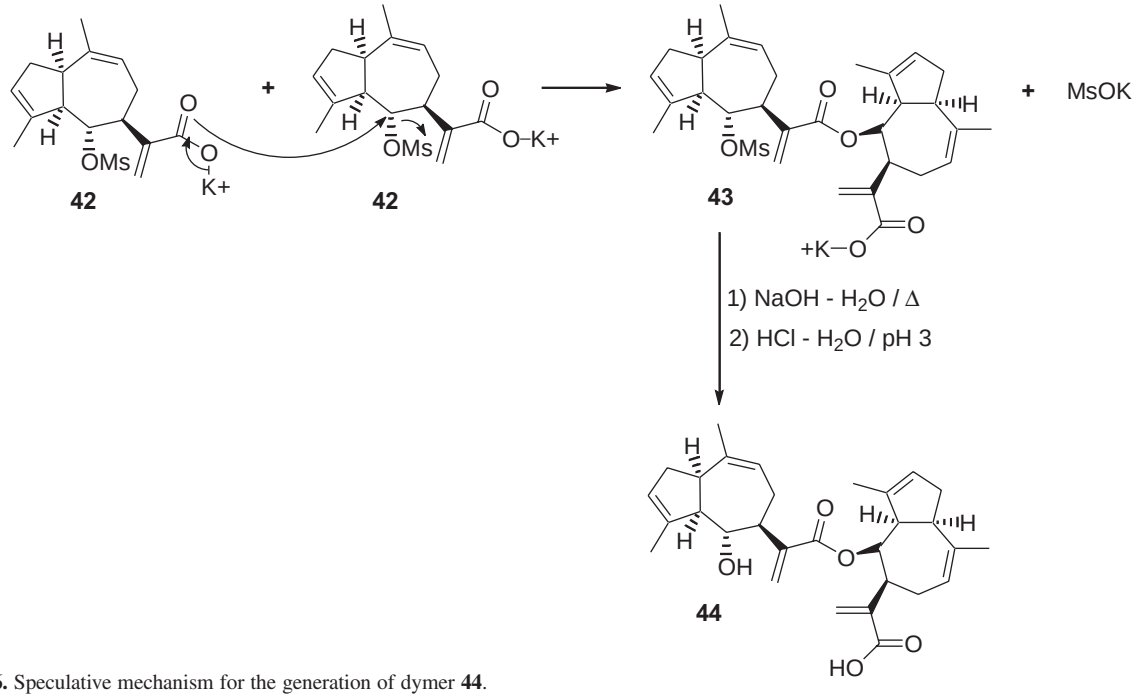
Initially, some experiments were accomplished with isoeremanthine (**10**), varying concentrations and times of reaction, in order to verify the ideal conditions for the

Table 3. Reactions of lactonic fusion inversion of models **8-13**

Exp.	Starting Materials	Reactions of opening of the lactonic ring[a]		Reactions of lactonic fusion inversion	
		Time (min)	Product	Solvent	Products (% - Proportion)[b]
1	 **8**	1440	 **31**	THF	 **8** + **32** (92% - 1 : 1)
2	 **9**	1440	 **33**	THF	 **9** + **34** (94% - 30 : 1)
3	 **10**	5	 **35**	THF	 **10** + **36** (92% - 6 : 1)
4	 **11**	60	 **37**	THF	 Products of Polymerization and Decomposition **11**: C_6-Hβ **38**: C_6-Hα (46% - 1 : 1) (Probable products)
5	 **12**	5	 **39**	THF	 **12** + **40** (89% - 3 : 1)
6	 **13**	10	 **41**	DMSO	 **17** + **27** (73% - 5 : 3)
7	 **13**	10	 **41**	THF	 **17** + **28** (91% - 5 : 6)

[a] All hydrolysis reactions were performed at room temperature, except in the Exp. 1-2, in which the reaction was initiated at room temperature for 23 h and then was heated at reflux for more 1 h to finish it. [b] The proportion of products was measured by integrals relative to the signals of C13-H at the ^{1}H NMR spectra of crude products.

reaction of lactonic fusion inversion. The choice of substance **10** to study the optimization of this reaction was due to the easy access from eremanthine (**1**) in just a step. In one of the experiments in which the lactonic inversion reaction was executed with 0.1 mol L^{-1} solution, it was obtained 6-*epi*-isoeremanthine (**36**) in mixture with a subproduct identified by ^{1}H NMR as the dymer **44**. The proportion of these two substances was 5:1 in favor of 6-*epi*-isoeremanthine (**36**). Substance **44** resulted from an intermolecular reaction of nucleophilic substitution between two molecules of carboxylate **42**, as speculative mechanism outlined in Scheme 6. The main chemical shifts for the hydrogens of dymer **44** observed in its ^{1}H NMR spectrum are shown in Table 5.



Scheme 6. Speculative mechanism for the generation of dymer **44**.

As the hydroazulene system has different conformations, we display in Table 6 conformational diagrams of the seven-membered rings that command the geometry of this system in study, for the models **8**-**13** and their respective products of lactonic fusion inversion, obtained with the MM2 program.[16] In Table 7 are depicted the torsion angles for these substances obtained in the MOPAC program.[16] The seven-membered rings presented in Table 6 were analyzed in the form of two different models: the cycloheptane and cycloheptene. These models can present themselves in the basic conformations such as chair (C), twist-chair (TC), boat (B) and twist-boat (TB).[9]

The substance **11** (Exp. 4 - Table 3) was totally unstable to conditions of lactonic fusion inversion. After the end of reaction, it was verified the formation of an insoluble organic pellicle at surface of solution, with aspect of a polymeric product. This supposed polymeric product was removed from the reaction middle by filtration and resulting mixture was extracted with organic solvent. It was obtained a product with moderate yield (46%) that was submitted to ^{1}H NMR. At the spectrum were observed the singlets of acetate group and C14-H at δ 2.01 and 1.69 ppm, respectively. With the enlargement of spectrum signals between δ 6.50 and 3.50 ppm it was possible to visualize and to attribute by attempts the signals of C15-H and C9-H to the multiplets at δ 5.30 - 4.80 ppm and the methylenes of γ-lactone to the superposed doublets at δ 6.30 - 6.10 and δ 5.60 - 5.35 ppm. A broad doublet at δ 4.19 ppm with coupling constant of 5.5 Hz suggested the presence of a γ-lactone with *cis* fusion. After experiment to obtain the ^{1}H NMR spectrum, it was made a TLC in which was detected decomposition of the material submitted to NMR, due to the presence of several stains on the plate.

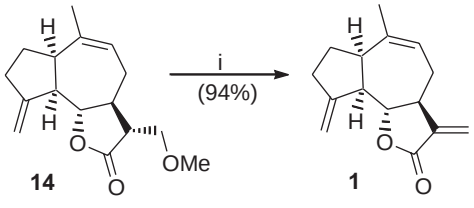
The carboxylic salt **41** was not much soluble in the solvent THF that we chose to study the reaction of lactonic fusion inversion on the models presented in Table 3. Due to this property we performed the Experiment 6 (Table 3), in which the reaction was executed with DMSO. The reduction in the yield of crude product at this reaction was attributed to losses in the partition phase due to the high polarity of the used solvent (DMSO). Moreover, it was verified a reduction in the conversion rate to epimeric product **27**. The ^{1}H NMR spectrum of crude product from Experiment 6 was identical to that previously obtained in the stage of methanol elimination on diol **21** (see Scheme 1 - step **ii**), from where it was confirmed that the subproduct obtained in that reaction was the epimer **27**. At the Experiment 7 (Table 3) this reaction was performed with THF and we obtained the epimer **28**, with *cis* lactonic fusion, in a double proportion of that obtained at the Exp. 6. Surprisingly, the acetate protection group stayed intact at the product **28** [δ 2.00 (s, 3H, -OCOCH$_3$) and 5.09 (m, 1H, C9-H) - ^{1}H NMR], suggesting that hydrolysis of this protection group in the solvent THF occurs in a slower rate than the one of the acetate at the substance **13**.

After verification that the configuration inversion on C-6 position of substance **17** could be done directly, starting from diol **21** at the stage of methanol elimination, we

Table 4. Selected chemical shifts for the hydrogens of starting materials and products of the reactions of lactonic fusion inversion at the ^{1}H NMR spectra

Exp.	Starting Materials and Products	Hydrogens [δ (Multiplicity, J / Hz)]				
		H-6	H-9	H-13	H-14	H-15
1	**8**	4.05 (m) 3.64 (m)	5.55 - 5.35 (m)	6.20 - 6.05 (m) 5.55 - 5.35 (m)	1.78 (bs) 1.69 (bs)	1.13 (d, 6.4) 0.92 (d, 6.4)
	32	4.16 (m)	4.25 - 4.10 (m)	7.26 (d, 2.2) 7.24 (d, 2.4)	-	-
2	**9**	4.17 (t, 10.5) 4.02 (dd, 9.3 and 10.2) 3.81 (t, 9.9)	-	6.18 (d, 3.6) 6.15 (d, 3.3) 6.13 (d, 3.5) 5.47 (d, 3.2) 5.43 (d, 3.1) 5.38 (d, 3.2)	0.97 (d, 7.2) 0.95 (d, 6.2)	1.17 (d, 6.4) 1.16 (d, 6.2)
	34	4.85 - 4.75 (m)	-	6.35 - 6.31 (m) 5.55 (d, 2.6) 5.49 (d, 2.7)	-	-
3	**10**	4.02 (dd, 8.9 and 10.7)	5.43 (m)	6.18 (d, 3.4) 5.46 (d, 3.1)	1.77 (bs)	1.91 (bs)
	36	4.78 (bd, 8.0)	5.21 (m)	6.24 (d, 2.1) 5.58 (d, 1.9)	1.63 (d, 1.3)	1.74 (d, 1.6)
4	**11**	3.68 (dd, 9.6 and 10.5)	5.24 (dd, 1.3 and 5.5)	6.10 (d, 3.4) 5.34 (d, 3.1)	1.82 (d, 1.2)	5.16 (d, 1.1) 5.08 (d, 1.1)
	38	4.19 (bd, 5.5)	5.30 - 4.80 (m)	6.30 - 6.10 (m) 5.60 - 5.35 (m)	1.69 (bs)	5.30 - 4.80 (m)
5	**12**	4.02 (t, 10.2)	-	6.13 (d, 3.5) 5.41 (d, 3.2)	0.96 (d, 7.2)	1.34 (s)
	40	4.12 (d, 6.4)	-	6.24 (bs) 5.64 (bs)	-	-
6	**17**	3.85 (dd, 9.9 and 10.7)	4.32 (m)	6.20 (d, 3.4) 5.50 (d, 3.1)	1.81 (d, 1.2)	1.27 (s)
	27	4.78 (bd, 5.4)	4.24 (m)	6.38 (bs) 5.63 (bs)	-	-
7	**13**	3.85 (dd, 10.2 and 10.8)	5.39 (dd, 2.0 and 4.7)	6.18 (d, 3.3) 5.45 (d, 3.1)	1.72 (bs)	1.27 (s)
	28	4.79 (bd, 5.6)	5.09 (m)	6.37 (bs) 5.62 (bs)	-	-

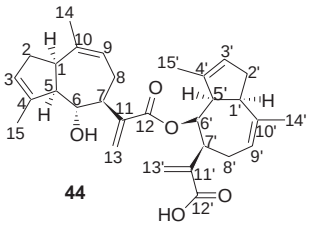
decided to investigate this reaction with more details. Initially, we planned to substitute DMF commonly employed at the reactions of methanol elimination on eremanthine derivatives, for a polar aprotic solvent of lower ebullition point, the acetonitrile. Such procedure was idealized in order to facilitate the isolation of product since the use of DMF, with high ebullition point, turned more difficult the purification process of the elimination products. The starting material initially used on the methanol elimination with the new solvent (CH_3CN) was the methoxy derivative **14**, due to the easy access from eremanthine (**1**) in just a stage. The reaction was executed at the conditions described in Scheme 7. After the time of reaction, crude product was extracted and it was verified by TLC total



Scheme 7. Reagents and conditions: *i*) 4 mol L^{-1} NaOH (5.5 equiv), CH_3CN (reflux - 5 h).

regeneration of eremanthine (**1**) with excellent yield and chromatography purity. With this satisfactory result, we performed the elimination reaction with diol **21** (Scheme 8). After the time of reaction, crude product was extracted and then submitted to ^{1}H NMR. The spectrum showed the

Table 5. Selected chemical shifts for the hydrogens of dymer **44** (^{1}H NMR)



44

R_f = 0.38 (15% EtOAc / hexane)

Hydrogens	δ (Multiplicity, J / Hz)
H_a-13'	6.47 (dd, 1.0 and 2.6)
H_a-13	6.18 (d, 3.5)
H_b-13'	5.56 (dd, 1.0 and 2.6)
H-3	5.51 (m)
H_b-13	5.46 (d, 3.1)
H-9	5.21 (m)
H-3'	4.88 (m)
H-9'	4.86 (m)
H-6'	4.43 (bd, 10.4)
H-6	4.02 (dd, 8.9 and 10.2)
H-15'	1.75 (bs)
H-15	1.67 (bs)
H-14	1.57 (bs)
H-14'	1.57 (bs)

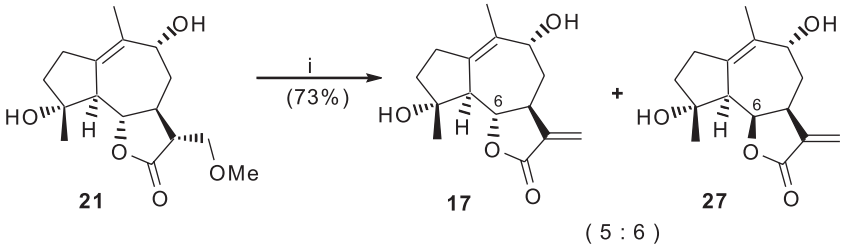
signals relative to the mixture of epimers **17** and **27**, in a proportion of 6:5 in favor of epimer **27** with *cis* lactonic fusion. This result does suggest the use of acetonitrile as solvent, at the stage of methanol elimination on diol **21** for generation of epimer **27**. The use of DMF generated this substance in relation to diol **17** with *trans* lactonic fusion in a respective proportion of only 1:3 (see Scheme 1).

Stereochemical considerations

From the results described in Table 3 for the reactions of lactonic fusion inversion of models **8**-**13**, we can deduce that intramolecular nucleophilic substitution, responsible for configuration inversion on C-6 position of the γ-lactones in study depends on geometric factors, intrinsic to molecular structure of each substance, that favor the attack of carboxylate to carbon containing the mesylate leaving group. Besides the favorable geometry of reactive substrate to attack by carboxylate, it should also be considered the stability of final product with *cis* lactonic fusion as well as the conformational interconversions, whose transitions from a particular form to another one generally involve high energies.[23] Therefore, the low proportions of products with *cis* lactonic fusion obtained in the Exp. 2, 3 and 5 (Table 3) were attributed to conformational effects in the hydroazulene system that turned the C-6 position of substrates disfavored to attack by carboxylate, as well as to the changes of conformation in the system, passing from stableer conformations in the substrates to conformers with higher steric energies at products with *cis* lactonic fusion, according to theoretical calculations obtained with MM2 program.[16] Due to the few steric interactions observed in the model **11** (Exp. 4 - Table 3), the probable successive intermolecular reactions by attack of carboxylate to C-6 position at the reactive intermediate mesylate, resulted in the formation of supposed polymeric subproducts obtained in this reaction. The good conversion rate to product with *cis* lactonic fusion, obtained by the model **8** (Exp. 1 - Table 3) was attributed to favorable geometry of the carboxylates to attack the C-6 positions of reactive intermediates containing the mesylate leaving groups, as well as the generation of products (**32a**-**b**) with less steric interactions than the substrates (**8a**-**b**). The best result obtained by the model **13** (Exp. 7 - Table 3) was attributed to favorable geometry of the system for the reaction of lactonic inversion and for not having conformational interconversion in the seven-membered ring, during the transformation process of the substrate (**13**) into product with *cis* lactonic fusion (**28**) (see Table 6).

Conclusions

The results obtained in this work have demonstrated that allylic acetate **13** emerged as a promising substance for subsequent preparation of its epimer **28** in a multigram scale. Compound **28** was obtained with a good conversion rate starting from substrate **13** and it was stable in the reaction conditions of lactonic inversion. Moreover we

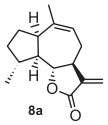
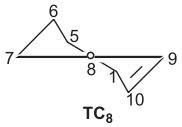
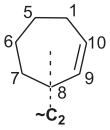
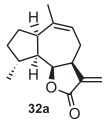
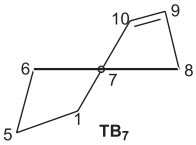
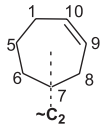
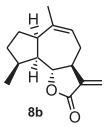
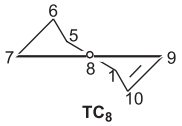
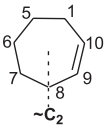
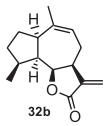
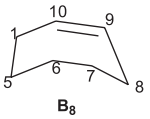
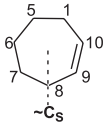
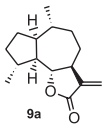
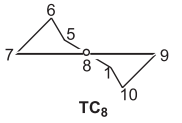
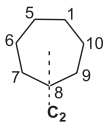
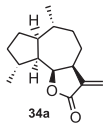
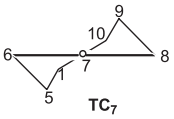
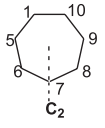
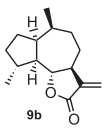
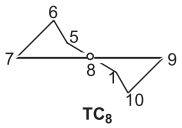
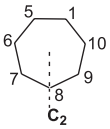
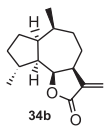
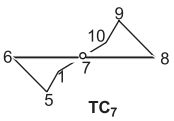
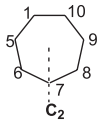
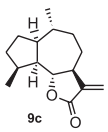
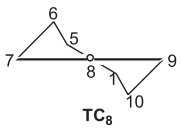
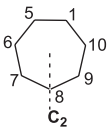
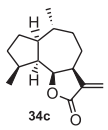
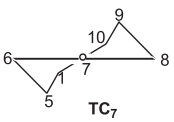
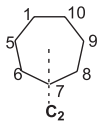
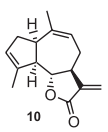
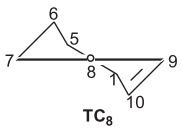
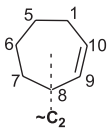
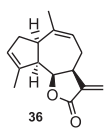
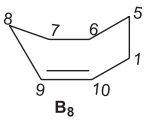
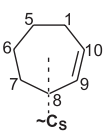
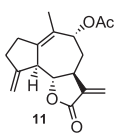
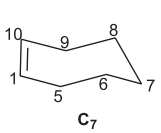
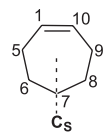
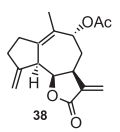


21 **17** **27**

(5 : 6)

Scheme 8. Reagents and conditions: *i*) 4 mol L^{-1} NaOH (5.5 equiv), CH_3CN (reflux - 3 h).

Table 6. Conformational diagrams of the seven-membered rings for the hydroazulene system of models **8**-**13** and their respective products of lactonic fusion inversion

Starting Materials	Conformational Diagrams[a] for the Seven-membered Rings		Products	Conformational Diagrams[a] for the Seven-membered Rings	
 **8a**	 **TC_8**	 **$\sim C_2$**	 **32a**	 **TB_7**	 **$\sim C_2$**
 **8b**	 **TC_8**	 **$\sim C_2$**	 **32b**	 **B_8**	 **$\sim C_S$**
 **9a**	 **TC_8**	 **C_2**	 **34a**	 **TC_7**	 **C_2**
 **9b**	 **TC_8**	 **C_2**	 **34b**	 **TC_7**	 **C_2**
 **9c**	 **TC_8**	 **C_2**	 **34c**	 **TC_7**	 **C_2**
 **10**	 **TC_8**	 **$\sim C_2$**	 **36**	 **B_8**	 **$\sim C_S$**
 **11**	 **C_7**	 **C_S**	 **38**	**C_7**	**C_S**
12	**C_5**	**C_S**	**40**	**C_7**	**C_S**
13	**C_7**	**C_S**	**28**	**C_7**	**C_S**

[a] The subscript used in the symbol defining a particular conformation [chair (C), twist-chair (TC), boat (B) and twist-boat (TB)] indicates the atom sectioned by the symmetry element [C_2-axis (C_2), pseudo-C_2 axis (~C_2), C_S plane (C_S) or pseudo-C_S plane (~C_S)].

Table7. Selected torsion angles for the hydroazulene system of models **8**-**13** and their respective products of lactonic fusion inversion

Substances	Bonds/Torsion Angles (Degrees)								
	O6-C6-C7-C11	C4-C5-C1-C2	C10-C1-C5-C6	C9-C10-C1-C5	C8-C9-C10-C1	C7-C8-C9-C10	C6-C7-C8-C9	C5-C6-C7-C8	C1-C5-C6-C7
8a	-19.653	29.181	35.910	-67.890	115.557	-51.952	-34.736	93.719	-67.002
32a	8.900	30.314	36.275	22.140	-4.364	-64.627	63.447	11.379	-69.646
8b	-20.421	29.270	32.400	-66.570	114.277	101.215	-36.745	93.167	-62.197
32b	7.223	37.062	41.006	17.673	-3.824	-62.886	64.439	9.106	-69.852
9a	-18.464	31.363	38.756	-51.697	83.087	-48.801	-34.654	95.769	-72.861
34a	16.583	39.592	50.209	-33.164	63.141	-97.571	54.204	22.119	-68.249
9b	-15.915	30.003	39.305	-61.679	90.383	-40.811	-43.108	98.970	-68.353
34b	16.288	40.381	53.720	-42.746	71.480	-97.902	52.152	21.937	-66.677
9c	-17.548	33.722	37.620	-52.758	83.734	-44.906	-38.223	96.674	-69.709
34c	16.200	42.914	51.823	-34.707	63.367	-97.105	54.622	21.717	-68.385
10	-20.739	18.916	27.160	-62.935	116.450	-51.891	-37.375	92.614	-58.049
36	-15.085	-8.346	-17.887	-39.365	6.459	70.882	-61.762	-20.101	68.046
11	-25.899	-2.147	53.779	1.644	-53.627	70.469	-74.283	83.929	-80.562
38	26.854	6.108	65.491	-6.583	-62.755	79.546	-49.662	36.763	-59.513
12	-26.933	-30.800	79.967	-81.581	28.094	42.996	-89.841	83.268	-65.864
40	23.742	-10.162	95.543	-45.318	-41.517	93.353	-58.920	31.171	-59.752
13	-25.422	-13.882	42.692	5.183	-47.488	66.467	-77.955	86.293	-73.421
28	27.849	10.432	66.636	-6.083	-63.194	78.248	-49.113	38.366	-61.952
27	27.810	10.722	67.423	-7.076	-64.127	81.399	-51.279	38.295	-61.198

verified, from this study, that allylic acetate **28** can also be easily obtained starting from diol **21**, at the stage of methanol elimination. For this method it was obtained the epimeric allylic alcohols **17** and **27** in a proportion of 5:6 in favor of the substance **27** with *cis* lactonic fusion, with the use of acetonitrile as the solvent of reaction. Although this mixture of epimeric allylic alcohols has presented separation problems for column chromatography of silica gel, due to the high polarity and proximity of their R_f, their correspondent allylic acetates **13** and **28** were easily separated. Allylic acetate **28**, with *cis* lactonic fusion, has the necessary structural requirements to unchain the rearrangements preconized by the hypothesis of pseudoguaianolides biogenesis,[24] in other words, α-hydroxy group at C-4, oxygen at β-position at C-6 and a potential cationic center at C-1. These results allow us to idealize the possibility of obtaining the substance **28** for one of the two epimerization methods developed in this work, for an eventual study of biomimetic transformation of guaianolides into pseudoguaianolides.

Experimental

Infrared spectra (IR) were recorded on a Perkin-Elmer 1420 spectrophotometer, using either thin films on NaCl plates (film) or KBr discs. NMR spectra were recorded on a Bruker AC-200 (^{1}H: 200 MHz and ^{13}C: 50.3 MHz) spectrometer. $CDCl_3$ was used as the solvent and TMS as internal standard. Coupling constants (*J*) are reported in Hertz (Hz). Multiplicities are indicated as s (singlet), bs (broad singlet), d (doublet), bd (broad doublet), t (triplet), m (multiplet), dd (double doublet). Assignment of the hydrogens was made with base on the Homonuclear Correlation Spectra ^{1}Hx^{1}H-COSY. Multiplicities of the signals of carbon-13 were obtained using a DEPT sequence. Low resolution mass spectrum of allylic alcohol **16** was obtained at 70 eV, for electrons impact, on a VG AutoSpecQ spectrometer. Thin layer chromatography was performed on aluminium sheets coated with 60 F_{254} silica. Visualization of the substances on the plates of TLC was accomplished under lamp of ultraviolet light (UV) and/or for contact of the plates with silica gel impregnated with iodine and/or spraying with 2% $Ce(SO_4)_2$ in 2 mol L^{-1} H_2SO_4 and subsequent heating. Purifications and isolations by column chromatography were performed with silica gel (230-400 mesh). Solvents and reagents were dried and purified by the usual methods.[25] Hydrogenations were carried out using a Parr apparatus. Melting points were taken on a Kofler apparatus and are uncorrected. The values of steric energies and the three-dimensional structures of substances presented in this paper were obtained by using MM2 and MOPAC programs, minimizing energy to minimun RMS gradient of 0.100 and displaying each iteration.[16]

*(11S)-Guai-9-eno-4β(H)-13-methoxy-12,6α-lactone (**22a**) and (11S)-Guai-9-eno-4α(H)-13-methoxy-12,6α-lactone (**22b**)*

Eremanthine methoxy derivative (**14**) (0.074 g, 0.282 mmol), 10% Pd-C (0.015 g, 0.0141 mmol), ethanol (7.5 mL) and hydrogen (40 psi) were shaken in a Parr apparatus at

room temperature for 1 h. The mixture was filtered and concentrated in vacuum. It was obtained a colourless oil (0.069 g, 93%) characterized as a mixture of diastereoisomers **22a**-**b**. R_f 0.50 (25% EtOAc / hexane). IR (film) ν_{max} / cm^{-1}: 2920, 1780, 1765, 1660, 1450, 1380, 1320, 1180, 1100, 1000, 760. ^1H NMR ($CDCl_3$, partial assignment): δ 5.60 - 5.30 (m, 2H, 2 H-9), 4.02 (dd, *J* 9.8 and 11.7 Hz, 1H, H-6), 3.75 - 3.50 (m, 5H, H-6 and 2 H-13), 3.34 (s, 3H, -OCH_3), 3.33 (s, 3H, -OCH_3), 2.70 - 0.80 {34H [1.77 (bs, H-14), 1.68 (bs, H-14), 1.13 (d, *J* 6.6 Hz, H-15), 0.94 (d, *J* 6.2 Hz, H-15)]}.

*(11S)-Guaia-4β(H),10β(H)-13-methoxy-12,6α-lactone (**23a**); (11S)-Guaia-4β(H),10α(H)-13-methoxy-12,6α-lactone (**23b**) and (11S)-Guaia-4α(H),10β(H)-13-methoxy-12,6α-lactone (**23c**)*

Eremanthine methoxy derivative (**14**) (0.052 g, 0.198 mmol), 10% Pd-C (0.021 g, 0.0198 mmol), ethanol (3.0 mL) and hydrogen (60 psi) were shaken in a Parr apparatus at room temperature for 4 h. The mixture was filtered and concentrated in vacuum. It was obtained a colourless oil (0.051 g, 96%) characterized as a mixture of diastereoisomers **23a**-**c**. R_f 0.52 (25% EtOAc / hexane). IR (film) ν_{max} / cm^{-1}: 2920, 1775, 1460, 1180, 1100, 1000. ^1H NMR ($CDCl_3$, partial assignment): δ 4.20 - 4.10 (m, 1H, H-6), 4.01 (t, *J* 9.5 Hz, 1H, H-6), 3.67 (m, 1H, H-6), 3.62 (m, 6H, 3 H-13), 3.33 (s, 9H, 3 -OCH_3), 2.70 - 0.80 {60H [1.10 (d, *J* 6.3 Hz, H-15), 1.09 (d, *J* 6.4 Hz, H-15), 0.91 (d, *J* 6.1 Hz, H-14)]}.

*Guaia-9,11(13)-dieno-12,6α-lactone (**8**) and Guai-11(13)-eno-12,6α-lactone (**9**)*

*General procedure for preparation of α-methylene-γ-lactones **8** and **9***

A solution of appropriate methoxy derivative **22** / **23** (0.153 mmol) in DMF (1.0 mL) and aqueous 4 mol L^{-1} NaOH (0.2 mL, 0.841 mmol) was heated at reflux during 2 h for the reaction with methoxy derivative **22** and 6 h for the reaction of methoxy derivative **23**. After the respective times of reaction, it was allowed to cool at room temperature and aqueous 10% (v/v) HCl was added dropwise until pH 3. EtOAc (30 mL) was added and solution was washed with H_2O (2 × 30 mL). The organic layer was separated and aqueous phases were extracted with EtOAc (2 × 30 mL). The organic phases were dried with Na_2SO_4, filtered and evaporated under reduced pressure. Purification by column chromatography eluted with hexane and 10% EtOAc / hexane gave:
*Guaia-9,11(13)-dieno-4β(H)-12,6α-lactone (**8a**) and Guaia-9,11(13)-dieno-4α(H)-12,6α-lactone (**8b**)* (0.025 g, 71%) as a colourless oil. R_f 0.70 (25% EtOAc / hexane). ^1H NMR ($CDCl_3$, partial assignment): δ 6.20 - 6.05 (m, 2H, 2 H-13), 5.55 - 5.35 (m, 4H, 2 H-13 and 2 H-9), 4.05 (m, 1H, H-6), 3.64 (m, 1H, H-6), 2.80 - 0.80 {32H [1.78 (bs, H-14), 1.69 (bs, H-14), 1.13 (d, *J* 6.4 Hz, H-15), 0.92 (d, *J* 6.4 Hz, H-15)]}.
*Guai-11(13)-eno-4β(H),10β(H)-12,6α-lactone (**9a**); Guai-11(13)-eno-4β(H),10α(H)-12,6α-lactone (**9b**) and Guai-11(13)-eno-4α(H),10β(H)-12,6α-lactone (**9c**)* (0.030 g, 84%) as a colourless oil. R_f 0.76 (50% EtOAc / hexane). IR (film) ν_{max} / cm^{-1}: 2920, 1760, 1460, 1260, 1150, 985. ^1H NMR ($CDCl_3$, partial assignment): δ 6.18 (d, *J* 3.6 Hz, 1H, H-13), 6.15 (d, *J* 3.3 Hz, 1H, H-13), 6.13 (d, *J* 3.5 Hz, 1H, H-13), 5.47 (d, *J* 3.2 Hz, 1H, H-13), 5.43 (d, *J* 3.1 Hz, 1H, H-13), 5.38 (d, *J* 3.2 Hz, 1H, H-13), 4.17 (t, *J* 10.5 Hz, 1H, H-6), 4.02 (dd, *J* 9.3 and 10.2 Hz, 1H, H-6), 3.81 (t, *J* 9.9 Hz, 1H, H-6), 2.90 - 2.65 (m, 1H, H-7), 2.65 - 2.45 (m, 1H, H-7), 2.45 - 2.20 (m, 1H, H-7), 2.20 - 0.80 {54H [1.17 (d, *J* 6.4 Hz, H-15), 1.16 (d, *J* 6.2 Hz, H-15), 0.97 (d, *J* 7.2 Hz, H-14), 0.95 (d, *J* 6.2 Hz, H-14)]}.

*Isoeremanthine (**10**)*

A solution of eremanthine (**1**) (0.200 g, 0.868 mmol), dry benzene (1.6 mL) and $BF_3.OEt_2$ freshly distilled (0.12 mL, 0.955 mmol) was stirred at room temperature and nitrogen atmosphere during 5.5 h. The mixture was diluted with $CHCl_3$ (30 mL) and washed with aqueous 5% $NaHCO_3$ (3 × 25 mL) and H_2O (2 × 25 mL). The organic layer was separated and aqueous phases were extracted with $CHCl_3$ (1 × 30 mL). The organic extracts were dried with Na_2SO_4, filtered and concentrated in vacuum. It was obtained a yellowish oil (0.164 g, 82%) identified as isoeremanthine (**10**). R_f 0.76 (50% EtOAc / hexane). IR (film) ν_{max} / cm^{-1}: 3010, 2910, 1760, 1660, 1625, 1440, 1375, 1305, 1260, 1230, 1145, 990, 960, 940, 815, 750, 665. ^1H NMR ($CDCl_3$, partial assignment): δ 6.18 (d, *J* 3.4 Hz, 1H, H-13), 5.52 (m, 1H, H-3), 5.46 (d, *J* 3.1 Hz, 1H, H-13), 5.43 (m, 1H, H-9), 4.02 (dd, *J* 8.9 and 10.7 Hz, 1H, H-6), 3.10 - 1.50 {13H [1.91 (bs, H-15), 1.77 (bs, H-14)]}. ^{13}C NMR ($CDCl_3$): δ 170.09 (C=O), 143.83 (C), 139.37 (C), 137.19 (C), 125.52 (CH), 119.51 (CH_2), 119.33 (CH), 86.06 (CH), 54.79 (CH), 47.79 (CH), 44.79 (CH), 37.92 (CH_2), 29.83 (CH_2), 27.85 (CH_3), 17.63 (CH_3).

*Guai-11(13)-eno-4α,15α,9α,10α-diepoxy-12,6α-lactone (**15**)*

Preparation of peracetic acid solution. H_2O_2 (30% - 25.4 mL) was added to a round bottom flask containing

glacial acetic acid (12.6 mL) and the mixture was stirred for 30 minutes. $CHCl_3$ (21 mL) was added and the mixture, kept in the dark, was vigorously stirred at room temperature for 24 h. The organic layer was separated and then used in the epoxidation reaction.

*Epoxidation of eremanthine (**1**).* Eremanthine (**1**) (0.300 g, 1.302 mmol) was dissolved in a solution of $AcO_2H/CHCl_3$ (21 mL), prepared as described above. The resulting solution was kept in the dark and stirred at room temperature for 96 h. The mixture was transferred to a separatory funnel and then washed with H_2O (1 × 30 mL), aqueous 5% $NaHCO_3$ (2 × 30 mL) and again with H_2O (1 × 30 mL). The organic layer was separated and the aqueous phases were extracted with $CHCl_3$ (3 x 35 mL). The organic extracts were dried with Na_2SO_4, filtered under activated charcoal and the solvent removed under reduced pressure to give diepoxide **15** as a colourless crystalline residue (0.274 g, 80%). R_f 0.40 (50% EtOAc / hexane). IR (KBr) ν_{max}/cm^{-1}: 2915, 1760, 1670, 1465, 1440, 1410, 1380, 1265, 1150, 1090, 985, 930, 880, 815, 760, 730. ^{1}H NMR ($CDCl_3$, partial assignment): δ 6.17 (d, *J* 3.4 Hz, 1H, H-13), 5.48 (d, *J* 3.2 Hz, 1H, H-13), 3.71 (dd, *J* 9.6 and 11.3 Hz, 1H, H-6), 3.30 - 1.10 {15H [3.14 (d, *J* 4.1 Hz, H-15), 3.05 (d, *J* 5.0 Hz, H-9), 2.89 (d, *J* 4.1 Hz, H-15), 1.37 (s, H-14)]}. ^{13}C NMR ($CDCl_3$): δ 169.54 (C=O), 138.58 (C), 119.67 (CH_2), 81.34 (CH), 65.72 (C), 63.29 (C), 61.41 (CH), 52.14 (CH), 49.92 (CH_2), 44.88 (CH), 40.73 (CH), 28.18 (CH_2), 28.06 (CH_2), 26.33 (CH_2), 26.24 (CH_3).

*Guaia-1(10),11(13)-dieno-4α,9α-dihydroxy-15-iodine-12,6α-lactone (**18**) and Guaia-1(10),11(13)-dieno-4α-hydroxy,9α-acetate-15-iodine-12,6α-lactone (**19**)*

A mixture of diepoxide **15** (0.270 g, 1.029 mmol), KI (0.188 g, 1.132 mmol), glacial acetic acid (0.88 mL, 15.435 mmol) and acetone (1.80 mL) was heated at reflux for 5 h. It was then allowed to cool, diluted with EtOAc (30 mL) and transferred to a separatory funnel. The solution was washed with H_2O (1 × 30 mL), aqueous 5% $NaHCO_3$ (1 × 30 mL), aqueous 5% $Na_2S_2O_3$ (1 × 30 mL) and again with H_2O (1 × 30 mL). The organic layer was separated and the aqueous phases were extracted with EtOAc (1 × 30 mL). The organic phases were dried with Na_2SO_4, filtered and concentrated in vacuum. It was obtained a crude product that was purified by column chromatography (50% EtOAc / hexane). It was obtained yellowish crystals (0.330 g, 82%) identified as iodohydrin **18**. R_f 0.16 (50% EtOAc / hexane); m. p. 119 - 120 °C (decomposition). IR (KBr) ν_{max} / cm^{-1}: 3510, 3400, 3030, 2940, 2880, 1760, 1665, 1410, 1315, 1220, 1175, 1135, 1040, 950. ^{1}H NMR ($CDCl_3$, partial assignment): δ 6.22 (d, *J* 3.3 Hz, 1H, H-13), 5.52 (d, *J* 3.1 Hz, 1H, H-13), 4.32 (dd, *J* 2.0 and 4.6 Hz, 1H, H-9), 3.85 (dd, *J* 9.9 and 11.2 Hz, 1H, H-6), 3.63 (dd, *J* 2.1 and 10.8 Hz, 1H, H-15), 3.50 - 3.20 (m, 2H, H-5 and H-7), 3.29 (d, *J* 10.8 Hz, 1H, H-15), 2.55 - 1.10 {11H [1.80 (bs, H-14)]}. ^{13}C NMR ($CDCl_3$): δ 168.32 (C=O), 138.13 (C), 134.47 (C), 130.80 (C), 120.09 (CH_2), 83.00 (CH), 81.03 (C), 72.21 (CH), 55.93 (CH), 41.66 (CH), 37.22 (CH_2), 33.03 (CH_2), 30.02 (CH_2), 22.78 (CH_3), 14.87 (CH_2).

Iodohydrin **18** (0.155 g, 0.397 mmol) was dissolved in acetic anhydride (2.70 mL) and to resulting solution was added pyridine (0.67 mL). The mixture was stirred at room temperature for 2 h and then diluted with EtOAc (20 mL), transferred to a beaker containing pricked ice and then stirred for 10 min. The aqueous phase was separated and organic layer was washed with aqueous 5% $NaHCO_3$ (1 × 20 mL) and H_2O (1 × 20 mL). The organic layer was separated and the aqueous phases were extracted with EtOAc (1 × 20 mL). The organic layers were dried with Na_2SO_4, filtered and concentrated in vacuum to give: *Allylic acetate **19*** (0.155 g, 90%) as a brownish oil. R_f 0.50 (50% EtOAc / hexane). IR (film) ν_{max} / cm^{-1}: 3500, 2940, 1770, 1730, 1440, 1375, 1240, 1140, 1040, 980, 960, 920, 820, 760, 735. ^{1}H NMR ($CDCl_3$, partial assignment): δ 6.23 (d, *J* 3.3 Hz, 1H, H-13), 5.49 (d, *J* 3.0 Hz, 1H, H-13), 5.40 (m, 1H, H-9), 3.87 (dd, *J* 9.9 and 11.2 Hz, 1H, H-6), 3.66 (dd, *J* 2.2 and 10.8 Hz, 1H, H-15), 3.40 - 3.20 (m, 1H, H-7), 3.31 (d, *J* 10.8 Hz, 1H, H-15), 3.14 (m, 1H, H-5), 2.40 - 1.15 {13H [2.05 (s, -OCOCH$_3$), 1.74 (bs, H-14)]}. ^{13}C NMR ($CDCl_3$): δ 170.36 (C=O), 168.81 (C=O), 137.67 (C), 137.25 (C), 130.15 (C), 120.15 (CH_2), 82.61 (CH), 81.00 (C), 73.36 (CH), 55.83 (CH), 42.58 (CH), 37.19 (CH_2), 30.37 (CH_2), 30.09 (CH_2), 22.51 (CH_3), 21.18 (CH_3), 14.84 (CH_2).

*Guaia-1(10),4(15),11(13)-trieno-9α-acetate-12,6α-lactone (**11**); Guaia-1(10),4(15), 11(13)-trieno-9α-hydroxy-12,6α-lactone (**16**) and (11S)-Guaia-4(15), 10(14)-dieno-9α-hydroxy-13-methoxy-12,6α-lactone (**24**)*

*General procedure for preparation of allylic derivatives **11**, **16** and **24***

To a botton round flask containing the appropriate iodohydrin **18** / **19** / **20** (0.355 mmol) it was added powdered zinc (0.348 g, 5.325 mmol), ethanol (5.50 mL) and glacial acetic acid (0.10 mL, 1.775 mmol). The mixture, under magnetic stirring, was heated at reflux for 30 min. After allowed to cool at room temperature, the mixture was filtered, washing the zinc with ethanol (20 mL). H_2O (50 mL) was added and then concentrated in vacuum. The concentrated mixture was extracted with

EtOAc (1 × 50 mL). The aqueous phase was separated and organic layer was washed with aqueous 5% $NaHCO_3$ (1 × 50 mL) and H_2O (1 × 50 mL). The organic layer was separated and aqueous phases were extracted with EtOAc (1 x 50 mL). The organic layers were dried with Na_2SO_4, filtered and concentrated in vacuum.

Allylic alcohol ***16*** (0.085 g, 98%) as a yellowish oil. R_f 0.40 (50% EtOAc / hexane). IR (film) ν_{max} / cm^{-1}: 3450, 2920, 1760, 1660, 1440, 1410, 1375, 1310, 1260, 1145, 980, 760. ^1H NMR ($CDCl_3$, partial assignment): δ 6.10 (d, *J* 3.3 Hz, 1H, H-13), 5.36 (d, *J* 3.1 Hz, 1H, H-13), 5.17 (bs, 1H, H-15), 5.07 (bs, 1H, H-15), 4.33 (dd, *J* 1.3 and 3.9 Hz, 1H, H-9), 3.80 - 3.40 {3H [3.68 (t, *J* 10.1 Hz, H-6)]}, 2.60 - 1.10 {10H [1.82 (bs, H-14)]}. ^{13}C NMR ($CDCl_3$): δ 170.03 (C=O), 149.26 (C), 140.19 (C), 138.31 (C), 132.72 (C), 117.51 (CH_2), 110.29 (CH_2), 82.13 (CH), 71.94 (CH), 50.80 (CH), 43.50 (CH), 32.30 (CH_2), 32.07 (CH_2), 29.48 (CH_2), 22.36 (CH_3). m/z (%): 246 (M^+, 14%), 228 (8), 213 (4), 185 (6), 157 (6), 149 (17), 133 (22), 123 (8), 107 (11), 91 (19), 83 (100), 71 (14).

Allylic acetate ***11*** (0.100 g, 98%) as a colourless oil. R_f 0.65 (50% EtOAc / hexane). IR (film) ν_{max} / cm^{-1}: 2940, 1770, 1740, 1660, 1445, 1370, 1240, 1135, 1020, 740. ^1H NMR ($CDCl_3$, partial assignment): δ 6.10 (d, *J* 3.4 Hz, 1H, H-13), 5.34 (d, *J* 3.1 Hz, 1H, H-13), 5.24 (dd, *J* 1.3 and 5.5 Hz, 1H, H-9), 5.16 (d, *J* 1.1 Hz, 1H, H-15), 5.08 (d, *J* 1.1 Hz, 1H, H-15), 3.68 (dd, *J* 9.6 and 10.5 Hz, 1H, H-6), 3.54 (bd, *J* 10.2 Hz, 1H, H-5), 3.30 (m, 1H, H-7), 2.70 - 1.10 {12H [2.05 (s, -$OCOCH_3$), 1.82 (d, *J* 1.2 Hz, H-14)]}. ^{13}C NMR ($CDCl_3$): δ 170.27 (C=O), 169.38 (C=O), 148.83 (C), 140.98 (C), 139.77 (C), 129.91 (C), 117.72 (CH_2), 110.84 (CH_2), 81.42 (CH), 73.82 (CH), 51.04 (CH), 44.85 (CH), 32.31 (CH_2), 32.03 (CH_2), 29.74 (CH_2), 22.09 (CH_3), 21.06 (CH_3).

The crude product obtained from iodohydrin **20** was filtered by column of silica gel (50% EtOAc / hexane) to give: *Allylic alcohol* ***24*** (0.090 g, 91%) as a colourless oil. R_f 0.25 (50% EtOAc / hexane). IR (film) ν_{max} / cm^{-1}: 3450, 2930, 1775, 1660, 1440, 1380, 1320, 1180, 1100, 910, 760. ^1H NMR ($CDCl_3$, partial assignment): δ 5.14 (d, *J* 2.3 Hz, 1H, H-15), 5.00 (bs, 2H, H-14 and H-15), 4.80 (bs, 1H, H-14), 4.48 (t, *J* 3.5 Hz, 1H, H-9), 3.86 (t, *J* 9.4 Hz, 1H, H-6), 3.63 (m, 2H, H-13), 3.45 (m, 1H, H-5), 3.34 (s, -OCH_3), 2.90 - 1.10 {10H [2.77 (m, H-7)]}. ^{13}C NMR ($CDCl_3$): δ 176.05 (C=O), 151.81 (C), 151.56 (C), 112.23 (CH_2), 108.74 (CH_2), 85.77 (CH), 74.39 (CH), 69.27 (CH_2), 59.29 (CH_3), 51.47 (CH), 47.53 (CH), 40.07 (CH_2), 38.95 (CH), 38.49 (CH), 32.73 (CH_2), 29.67 (CH_2). Literature:[17] R_f 0.27 (50% EtOAc / hexane). IR (KBr) ν_{max} / cm^{-1}: 3353, 1771, 1186. ^1H NMR (100 MHz, $CDCl_3$, partial assignment): δ 5.15 (d, *J* 2.5 Hz, 1H, H-15), 5.03 (bs, 1H, H-15), 5.01 (bs, 1H, H-14), 4.82 (bs, 1H, H-14), 4.49 (t, *J* 3.5 Hz, 1H, H-9), 3.88 (t, *J* 9.5 Hz, 1H, H-6), 3.66 (d, *J* 4.0 Hz, 2H, H-13), 3.37 (s, 3H, -OCH_3).

*Guaia-1(10),11(13)-dieno-4α,9α-dihydroxy-12,6α-lactone (**17**)*

A solution of diol **21** (0.100 g, 0.337 mmol), DMF (2.4 mL) and aqueous 4 mol L^{-1} NaOH (0.46 mL, 1.853 mmol) was heated at reflux for 2 h. The mixture was allowed to cool at room temperature and it was added dropwise an aqueous solution of 10% (v/v) HCl until pH 3. EtOAc (25 mL) was added and solution was washed with H_2O (2 × 30 mL). The organic layer was separated and the aqueous phases were extracted with EtOAc (3 × 30 mL). The organic phases were dried with Na_2SO_4, filtered and concentrated in vacuum. The crude product was purified by column chromatography of silica gel eluted with 80% EtOAc / hexane. It was obtained a colourless oil (0.067 g, 75%) identified by ^1H NMR as the α-methylene-γ-lactone **17** in mixture with other lactone later identified as the substance **27**. The proportion of these lactones was 3 : 1 in favor of the substance **17** (^1H NMR). *Substance* ***17***: R_f 0.13 (50% EtOAc / hexane). IR (KBr) ν_{max} / cm^{-1}: 3450, 2920, 1760, 1660, 1450, 1380, 1140, 990. ^1H NMR ($CDCl_3$, partial assignment): δ 6.20 (d, *J* 3.4 Hz, 1H, H-13), 5.50 (d, *J* 3.1 Hz, 1H, H-13), 4.32 (m, 1H, H-9), 3.85 (dd, *J* 9.9 and 10.7 Hz, 1H, H-6), 3.35 (m, 1H, H-7), 2.89 (m, 1H, H-5), 2.60 - 1.10 {14H [1.81 (d, *J* 1.2 Hz, H-14), 1.27 (s, H-15)]}.

*Guaia-1(10),4(15),11(13)-trieno-9α-acetate-12,6α-lactone (**11**) and Guaia-1(10),11(13)-dieno-4α-hydroxy,9α-acetate-12,6α-lactone (**13**)*

*General procedure for preparation of allylic acetates **11** and **13***

The appropriate allylic alcohol **16** / (**17**+**27**) (0.227 mmol) was dissolved in acetic anhydride (1.54 mL) and to resulting solution was added pyridine (0.38 mL). The mixture was stirred at room temperature for 2 h and then diluted with EtOAc (30 mL), transferred to a beaker containing pricked ice and then stirred for 10 min. The aqueous phase was separated and organic layer was washed with aqueous 5% $NaHCO_3$ (1 × 20 mL) and H_2O (1 × 20 mL). The organic layer was separated and aqueous phases were extracted with EtOAc (1 × 30 mL). The organic layers were dried with Na_2SO_4, filtered and concentrated in vacuum.

Allylic acetate ***11*** (0.062 g, 95%) as a colourless oil. R_f 0.65 (50% EtOAc / hexane).

The crude product obtained from the acetylation of epimeric mixture (**17**+**27**) was purified by column chromatography of silica gel eluted with $CHCl_3$ and EtOAc to give: *Allylic acetate **13*** (0.038 g, 54%) as a colourless oil. Crystallization in $CHCl_3$ yielded **13** as colourless crystals [m.p. 132 - 134 °C]. R_f 0.37 (50% EtOAc / hexane). IR (film) ν_{max} / cm^{-1}: 3500, 2940, 1775, 1735, 1670, 1440, 1375, 1240, 1140, 990, 960, 820, 735. ^{1}H NMR ($CDCl_3$, partial assignment): δ 6.18 (d, *J* 3.3 Hz, 1H, H-13), 5.45 (d, *J* 3.1 Hz, 1H, H-13), 5.39 (dd, *J* 2.0 and 4.7 Hz, 1H, H-9), 3.85 (dd, *J* 10.2 and 10.8 Hz, 1H, H-6), 3.14 (m, 1H, H-7), 2.90 (m, 1H, H-5), 2.60 - 1.10 {16H [2.03 (s, -$OCOCH_3$), 1.72 (bs, H-14), 1.27 (s, H-15)]}. ^{13}C NMR ($CDCl_3$): δ 170.49 (C=O), 169.24 (C=O), 138.67 (C), 138.22 (C), 129.12 (C), 119.64 (CH_2), 83.50 (CH), 80.18 (C), 73.65 (CH), 57.84 (CH), 42.27 (CH), 37.85 (CH_2), 30.61 (CH_2), 30.48 (CH_2), 22.59 (CH_3), 22.45 (CH_3), 21.21 (CH_3).

*General procedure for the reactions of lactonic fusion inversion of substances **8**-**13***

A common procedure is described for the reaction of lactonic fusion inversion of substance **8**. To a botton round flask containing the substance **8** (0.013 g, 0.056 mmol) an aqueous solution of 4% KOH (0.36 mL, 0.258 mmol) was added and it was left under magnetic stirring at the temperature and time indicated in Table 3 (Exp. 1). After total solubilization of the substrate, TLC revealed consumption of starting material. The mixture was concentrated under reduced pressure and then dried in high vacuum. The carboxylic salt was dissolved in THF (0.56 mL) and then put in a bath of ice at the temperature of 0 °C under magnetic stirring. Et_3N (0.055 mL, 0.392 mmol) and MsCl (0.026 mL, 0.336 mmol) were added to solution and after 1 h the bath of ice was removed and mixture was left at room temperature for 3 h. Soon afterwards, an aqueous solution of 0.2 mol L^{-1} NaOH (0.90 mL, 0.179 mmol) was added and the mixture was put in a bath at the temperature of 50 °C for 1 h. The mixture was allowed to cool at room temperature and an aqueous 10% (v/v) HCl was added dropwise until pH 3. It was diluted with EtOAc (20 mL) and then washed with H_2O (2 × 20 mL). The organic layer was separated and the aqueous phases were extracted with EtOAc (1 × 20 mL). The organic phases were dried with Na_2SO_4, filtered and concentrated in vacuum. It was obtained: crude product (0.012 g, 92%). ^{1}H NMR ($CDCl_3$): partial assignment for the substance **32** (see Table 4).

*Lactonic fusion inversion of substance **9*** (Exp. 2 - Table 3)

The reaction was executed following general procedure, using **9** (0.016 g, 0.068 mmol) and aqueous solution of 4% KOH (0.44 mL, 0.313 mmol). The dry carboxylic salt was dissolved in THF (0.68 mL) and it was added to resulting solution Et_3N (0.066 mL, 0.476 mmol) and MsCl (0.032 mL, 0.408 mmol). After the time of reaction, aqueous solution of 0.2 mol L^{-1} NaOH (1.09 mL, 0.218 mmol) was added and the mixture was warmed in a bath at 50 °C for 1 h. The mixture was neutralized with 10% (v/v) HCl until pH 3 and then extracted with EtOAc. It was obtained: crude product (0.015 g, 94%). ^{1}H NMR ($CDCl_3$): partial assignment for the substance **34** (see Table 4).

*Lactonic fusion inversion of substance **10*** (Exp. 3 - Table 3)

The reaction was executed following general procedure, using **10** (0.012 g, 0.052 mmol) and aqueous solution of 4% KOH (0.34 mL, 0.239 mmol). The dry carboxylic salt was dissolved in THF (2.40 mL) and it was added to resulting solution Et_3N (0.051 mL, 0.364 mmol) and MsCl (0.024 mL, 0.312 mmol). After the time of reaction, aqueous solution of 0.2 mol L^{-1} NaOH (0.83 mL, 0.166 mmol) was added and the mixture was warmed in a bath at 50 °C for 1 h. The mixture was neutralized with 10% (v/v) HCl until pH 3 and then extracted with EtOAc. It was obtained: crude product (0.011 g, 92%). Due to difference of polarity between the two substances of this mixture, we proceeded to purification by column chromatography of silica gel (20% EtOAc / hexane) and it was separated a fraction as a colourless oil, identified as 6-*epi*-isoeremanthine (**36**). R_f 0.69 (50% EtOAc / hexane). IR (film) ν_{max} / cm^{-1}: 3050, 2920, 2850, 1765, 1660, 1610, 1460, 1380, 1270, 1155, 820. ^{1}H NMR ($CDCl_3$, partial assignment): δ 6.24 (d, *J* 2.1 Hz, 1H, H-13), 5.58 (d, *J* 1.9 Hz, 1H, H-13), 5.52 (m, 1H, H-3), 5.21 (m, 1H, H-9), 4.78 (bd, *J* 8.0 Hz, 1H, H-6), 3.40 - 1.50 {13H [1.74 (d, *J* 1.6 Hz, H-15), 1.63 (d, *J* 1.3 Hz, H-14)]}.

*Lactonic fusion inversion of substance **11*** (Exp. 4 - Table 3)

The reaction was executed following general procedure, using **11** (0.011 g, 0.038 mmol) and aqueous solution of 4% KOH (0.25 mL, 0.175 mmol). The dry carboxylic salt was dissolved in THF (0.87 mL) and it was added to resulting solution Et_3N (0.037 mL, 0.266 mmol) and MsCl (0.017 mL, 0.228 mmol). After the time of reaction, aqueous solution of 0.2 mol L^{-1} NaOH (0.61 mL, 0.122 mmol) was added and the mixture was warmed in a bath at 50 °C for 1 h. The mixture was neutralized with 10% (v/v) HCl until pH 3, filtered to remove a supposed insoluble polymeric material and then extracted

with EtOAc. It was obtained: crude product (0.005 g, 46%). ^{1}H NMR ($CDCl_3$): partial assignment for the substance **38** (see Table 4).

*Lactonic fusion inversion of substance **12*** (Exp. 5 - Table 3)

The reaction was executed following general procedure, using **12** (0.009 g, 0.036 mmol) and aqueous solution of 4% KOH (0.23 mL, 0.166 mmol). The dry carboxylic salt was dissolved in THF (0.35 mL) and it was added to resulting solution Et_3N (0.035 mL, 0.252 mmol) and MsCl (0.017 mL, 0.216 mmol). After the time of reaction, aqueous solution of 0.2 mol L^{-1} NaOH (0.58 mL, 0.115 mmol) was added and the mixture was warmed in a bath at 50 °C for 1 h. The mixture was neutralized with 10% (v/v) HCl until pH 3 and then extracted with EtOAc. It was obtained: crude product (0.008 g, 89%). ^{1}H NMR ($CDCl_3$): partial assignment for the substance **40** (see Table 4).

*Lactonic fusion inversion of substance **13*** (Exp. 6 - Table 3)

The reaction was executed following general procedure, using **13** (0.030 g, 0.098 mmol) and aqueous solution of 4% KOH (0.63 mL, 0.451 mmol). The dry carboxylic salt was dissolved in DMSO (1.10 mL) and it was added to resulting solution Et_3N (0.096 mL, 0.686 mmol) and MsCl (0.045 mL, 0.588 mmol). After the time of reaction, aqueous solution of 0.2 mol L^{-1} NaOH (1.57 mL, 0.314 mmol) was added and the mixture was warmed in a bath at 50 °C for 1 h. The mixture was neutralized with 10% (v/v) HCl until pH 3 and then extracted with EtOAc. It was obtained: crude product (0.019 g, 73%). ^{1}H NMR ($CDCl_3$): partial assignment for the substance **27** (see Table 4).

*Lactonic fusion inversion of substance **13*** (Exp. 7 - Table 3)

The reaction was executed following general procedure, using **13** (0.007 g, 0.023 mmol) and aqueous solution of 4% KOH (0.15 mL, 0.106 mmol). The dry carboxylic salt was dissolved in THF (0.50 mL) and it was added to resulting solution Et_3N (0.022 mL, 0.161 mmol) and MsCl (0.011 mL, 0.138 mmol). After the time of reaction, aqueous solution of 0.2 mol L^{-1} NaOH (0.37 mL, 0.074 mmol) was added and the mixture was warmed in a bath at 50 °C for 1 h. The mixture was neutralized with 10% (v/v) HCl until pH 3 and then extracted with EtOAc. It was obtained: crude product (0.006 g, 91%). ^{1}H NMR ($CDCl_3$): partial assignment for the substance **28** (see Table 4).

Regeneration of α-methylene-γ-lactone by methanol elimination using CH_3CN as the solvent

*Eremanthine (**1**).* A solution of eremanthine methoxy derivative (**14**) (0.021 g, 0.080 mmol) in CH_3CN (0.52 mL) and aqueous 4 mol L^{-1} NaOH (0.11 mL, 0.44 mmol) was heated at reflux for 5 h. After allowed to cool at room temperature, aqueous 10% (v/v) HCl was added dropwise until pH 3. EtOAc (20 mL) was added and solution was washed with H_2O (2 × 20 mL). The organic layer was separated and aqueous phases were extracted with EtOAc (2 × 20 mL). The organic phases were dried with Na_2SO_4, filtered and concentrated in vacuum. It was obtained a brownish oil (0.017 g, 94%) characterized as eremanthine (**1**). *Eremanthine (**1**):* R_f 0.75 (50% EtOAc / hexane). IR (KBr) ν_{max} / cm^{-1}: 2910, 1760, 1655, 1440, 1405, 1380, 1315, 1255, 1130, 1060, 1005, 890, 820. ^{1}H NMR ($CDCl_3$, partial assignment): δ 6.17 (d, *J* 2.6 Hz, 1H, H-13), 5.50 (bd, *J* 7.3 Hz, 1H, H-9), 5.44 (d, *J* 2.3 Hz, 1H, H-13), 5.18 (bs, 1H, H-15), 5.01 (bs, 1H, H-15), 3.91 (t, *J* 9.3 Hz, 1H, H-6), 2.90 - 1.40 {12H [1.80 (bs, H-14)]}.^{13}C NMR ($CDCl_3$): δ 169.91 (C=O), 149.86 (C), 139.86 (C), 137.89 (C), 120.60 (CH), 119.30 (CH_2), 110.72 (CH_2), 83.10 (CH), 52.35 (CH), 46.86 (CH), 45.11 (CH), 30.37 (CH_2), 29.40 (CH_2), 28.94 (CH_2), 27.82 (CH_3).

*Mixture of epimers **17** and **27**.* A solution of diol **21** (0.012 g, 0.040 mmol) in CH_3CN (0.27 ml) and aqueous 4 mol L^{-1} NaOH (0.055 mL, 0.220 mmol) was heated at reflux for 3 h. After allowed to cool at room temperature, 10% (v/v) HCl was added dropwise until pH 3. EtOAc (20 mL) was added and solution was washed with H_2O (2 × 20 mL). The organic layer was separated and the aqueous phases were exhaustively extracted with EtOAc (3 x 20 mL). The organic phases were dried with Na_2SO_4, filtered and concentrated in vacuum. It was obtained a brownish oil (0.008 g, 73%) identified as a mixture of epimers **17** and **27** in a respective proportion of 5:6 (^{1}H NMR). R_f 0.13 (50% EtOAc / hexane). ^{1}H NMR ($CDCl_3$): partial assignment to epimers **17** and **27** (see Table 4).

Supplementary Information

This supplementary material displays some sterochemical aspects of the lactonic inversion reaction of models **8**-**13**. This material is available free of charge via the Internet at http://jbcs.sbq.org.br.

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UFRJ for the mass spectrum of allylic alcohol **16** and the referees as well as the JBCS editorial staff for helpful suggestions.

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Study of the Inversion Reaction of the Lactonic Fusion on Eremanthine Derivatives

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This supplementary material displays some stereochemical aspects of the lactonic fusion inversion presented in the main text of the article.

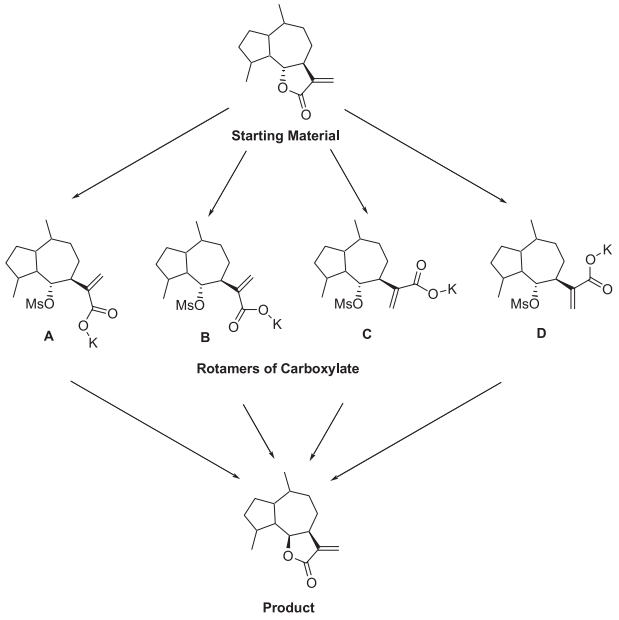
After opening the lactonic ring on starting materials with *trans* fusion in basic medium, followed by mesylation stage, the carboxylates can present themselves in different conformations as rotamers (Scheme S1). In order to compare the relative stabilities of the starting materials **8-13**, their correspondent reactive carboxylates (mesylates at C-6 position) and products with stereochemical inversion at the alkoxy carbon, we elaborated Table S1 containing the steric energies for these conformers. We used the MM2 program and then the three-dimensional structures of carboxylates from the models **8-13** in Table S1, displaying less steric interactions (Figures S1-9). After data analysis (shown in Table S1 and three-dimensional structures of carboxylates), we can assume:

(*i*) all conformers with less steric interactions of the opened lactonic rings, marked with asterisk in Table S1, have smaller steric energies than their respective substrates with *trans* lactonic fusion;

(*ii*) the two epimers **32a-b** have less steric interactions than their correspondent substrates **8a-b**. Such fact, associated with the favorable geometry of the carboxylates to nucleophylic attack on C-6 positions, observed in their three-dimensional structures (Figures S1-2), should have contributed to the better conversion rate of products with *cis* fusion (**32a-b**);

(*iii*) for the model **9**, the steric interactions on the conformers with *cis* lactonic fusion (**34a-c**) are larger than those of the respective substrates with *trans* fusion (**9a-c**), so that the reaction yielding products with configuration inversion on C-6 position should be disfavored, and this must have contributed for the lower conversion rate of epimeric products **34a-c**;

(*iv*) in model **10**, the steric interactions of epimer **36** are smaller than those of the substrate, however the boat



Scheme S1

(B_8) conformation of the final product is less stable than the twist-chair (TC_8) conformation of the initial substrate (Table 6 in the main text). Such fact should disfavor the formation of product **36,** leading to a larger proportion of product with *trans* lactonic fusion in relation to one with *cis* lactonic fusion;

(*v*) among the models submitted to conditions of lactonic fusion inversion, the carboxylate derived from allylic acetate **11** was the one which presented less steric interactions (Table S1). As this intermediate has few steric interations, the intermolecular nucleophylic substitution must have been favored to generate polymeric chains formation;

(*vi*) concerning model **12**, the steric interations between substrate and epimeric product (**40**) are similar. However, conformation changes between substrate (C_5) and product (C_7) (Table 6 in the main text) should be possibilities that disfavor the product formation with inversion of configuration on C-6 position;

(*vii*) the steric interactions on product **28** with *cis*

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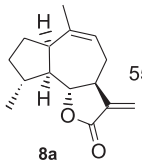
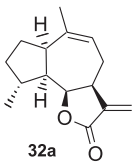
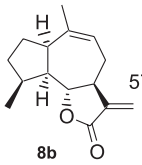
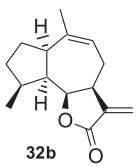
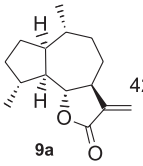
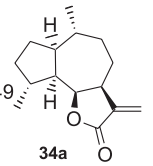
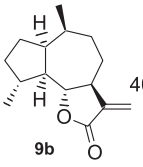
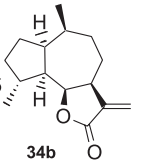
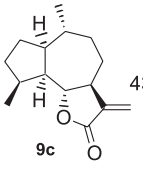
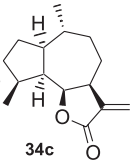
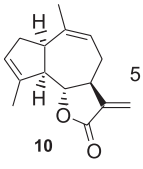
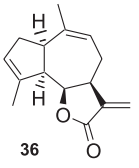
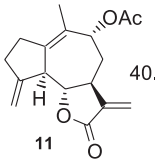
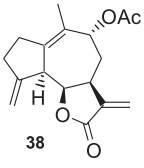
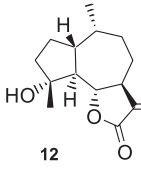
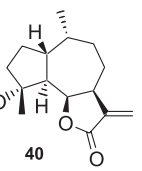
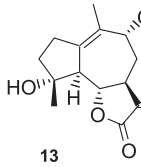
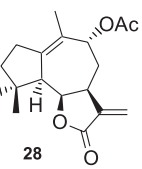
† Deceased in 1993

Table S1. Steric energies for starting materials, rotamers of carboxylates (**A**, **B**, **C**, **D**) and products of the reactions of lactonic fusion inversion of models **8-13**

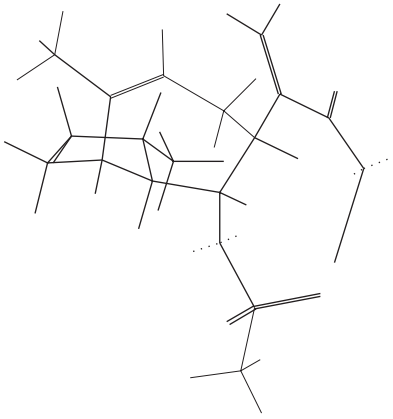
Starting Materials	Steric Energies (kcal mol^{-1})				
	Rotamers of Carboxylates[a]				Products
	A	B	C	D	
 **8a**	55.542	40.701*	43.066	50.299	53.165	39.200  **32a**
 **8b**	57.985	45.109*	47.555	54.315	53.645	39.044  **32b**
 **9a**	42.403	43.669	37.082*	44.239	51.276	45.849  **34a**
 **9b**	40.628	41.170	34.126*	43.098	50.072	44.565  **34b**
 **9c**	43.182	48.023	38.710*	42.930	46.006	45.797  **34c**
 **10**	51.798	52.637	46.693*	47.951	51.294	35.302  **36**
 **11**	40.424	34.522	27.437*	33.256	41.105	41.541  **38**
 **12**	44.986	35.064	34.897*	39.703	48.308	44.594  **40**
 **13**	43.254	39.163	32.300*	37.032	43.221	46.455  **28**

[a]Rotamers with lower energies are marked with asterisk

lactonic fusion are higher than the ones on substrate **13**. However, model **13** and its correspondent epimer **28** have the same conformations at the seven-membered ring (C_7) (Table 6 in the main text), so that, there is no process of conformational interconversion. This factor must have favored the best result obtained by this substance during the lactonic inversion reaction in relation to other models evaluated in this study.

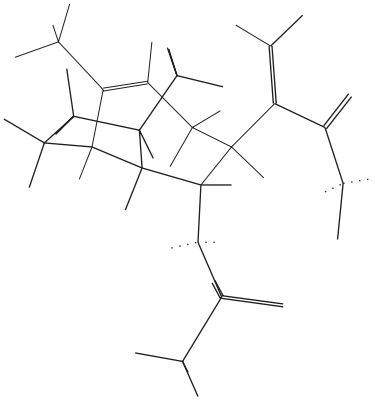
Qualitative graphics correlating steric energy (SE) with the coordinate of the lactonic inversion reaction to the substrates with *trans* lactonic fusion (**A**), reactive intermediate mesylates (**B**) and products with *cis* lactonic fusion (**C**) (Scheme S2) for the models **8-13** are depicted in Figures S10-12.

An intriguing result was obtained in the ^{1}H NMR spectrum of crude product from the reaction of lactonic fusion inversion of model **8** (Table 4 - Exp. 1, in the main text). After analysis of this spectrum we verified atypical values of chemical shifts for the hydrogens H-13 (deshielded) and H-9 (shielded) for the compounds **32,** not exhibited before in eremanthine derivatives. After analysis of three-dimensional structures of compounds **32a-b** with *cis* lactonic fusion (Figures S14-15), we verified space proximity of hydrogens H-13 with the deshielding area of double bond C9-C10 and the proximity of hydrogen H-9 with the shielding area of α-methylene-γ-lactone. The comparison of three-dimensional structures of compounds **32a-b** (Figures S14-15), that have double bond at C9-C10 and *cis* lactonic fusion, with the similar compound 6-*epi*-isoeremanthine (**36**) that differs from **32a-b** only in the unsaturation degree at C3-C4 (Figure S13), contributed to confirm this atypical data of ^{1}H NMR obtained with these compounds. In the three-dimensional structure of compound **36** (Figure S13) we verified that there is no space proximity of hydrogens H-9 and H-13 with the shielding/deshielding areas of double bonds mentioned for compounds **32a-b**. These conformational differences observed in the three-dimensional structures of the mentioned compounds must be the cause of atypical results obtained in their ^{1}H NMR spectra.



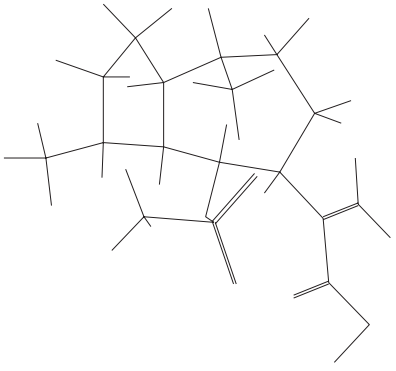
8a-A

Figure S1. Three-dimensional structure of reactive carboxylate (mesylate at C-6 position) of model **8a** with less steric interactions.



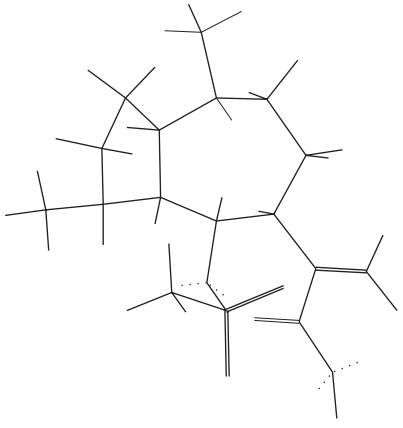
8b-A

Figure S2. Three-dimensional structure of reactive carboxylate (mesylate at C-6 position) of model **8b** with less steric interactions.



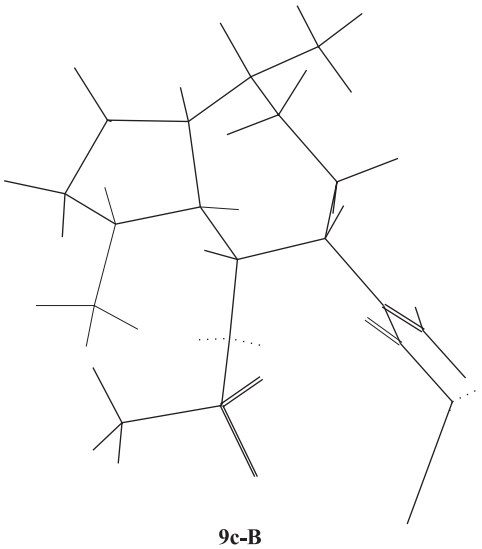
9a-B

Figure S3. Three-dimensional structure of reactive carboxylate (mesylate at C-6 position) of model **9a** with less steric interactions.



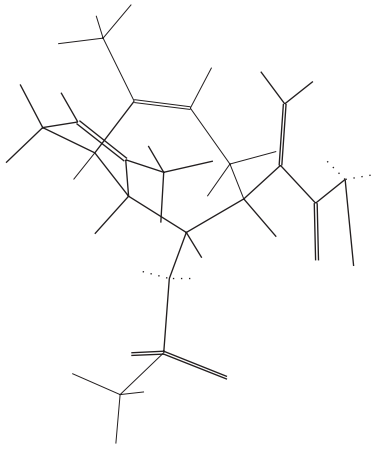
9b-B

Figure S4. Three-dimensional structure of reactive carboxylate (mesylate at C-6 position) of model **9b** with less steric interactions.



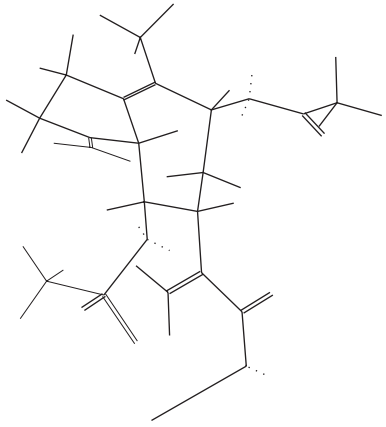
9c-B

Figure S5. Three-dimensional structure of reactive carboxylate (mesylate at C-6 position) of model **9c** with less steric interactions.



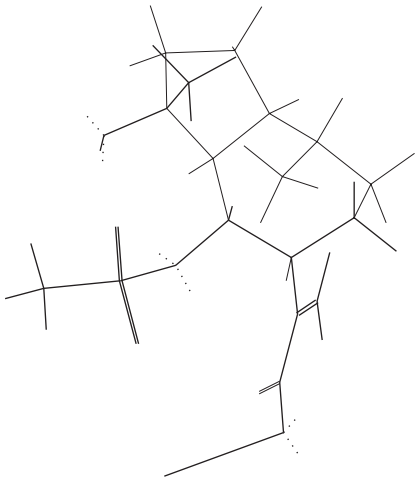
10-B

Figure S6. Three-dimensional structure of reactive carboxylate (mesylate at C-6 position) of model **10** with less steric interactions.



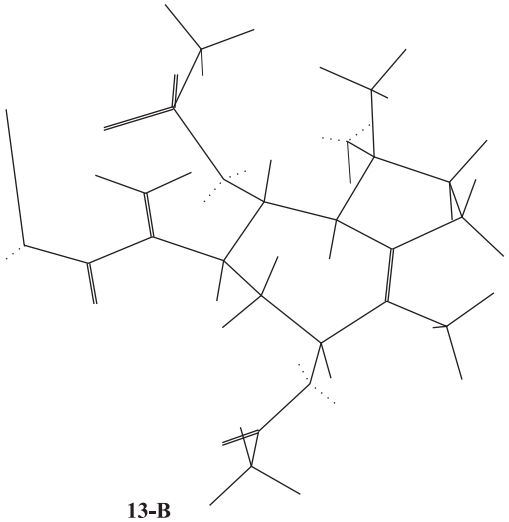
11-B

Figure S7. Three-dimensional structure of reactive carboxylate (mesylate at C-6 position) of model **11** with less steric interactions.



12-B

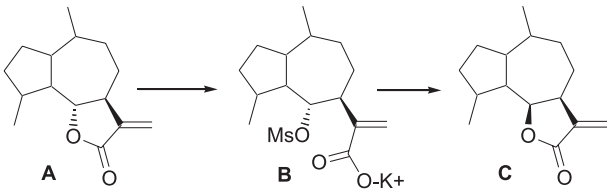
Figure S8. Three-dimensional structure of reactive carboxylate (mesylate at C-6 position) of model **12** with less steric interactions.



13-B

Figure S9. Three-dimensional structure of reactive carboxylate (mesylate at C-6 position) of model **13** with less steric interactions.

General Reaction



Scheme S2

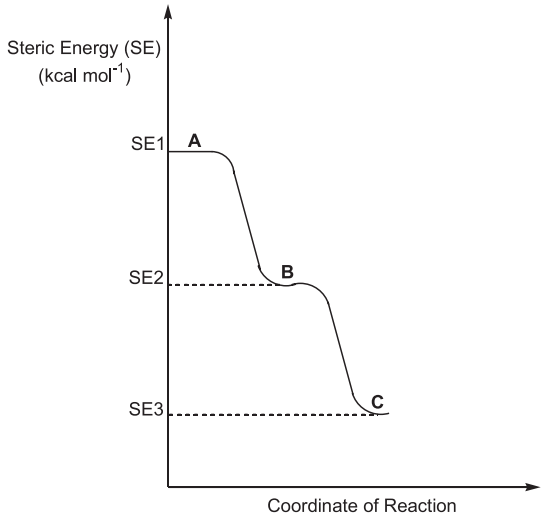


Figure S10. Qualitative graphic of steric energy (SE) versus coordinate of reaction for models **8a-b** and **10**.

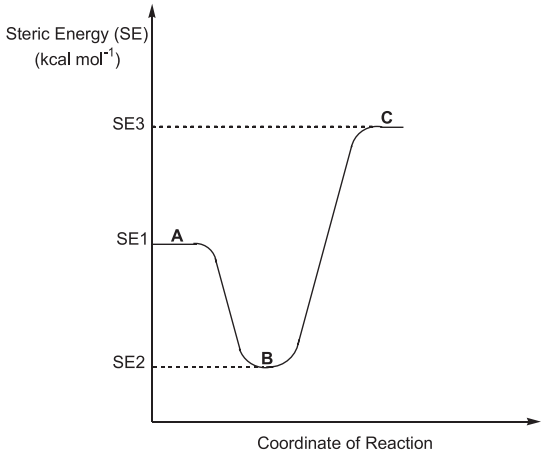


Figure S11. Qualitative graphic of steric energy (SE) versus coordinate of reaction for models **9a-c**, **11** and **13**.

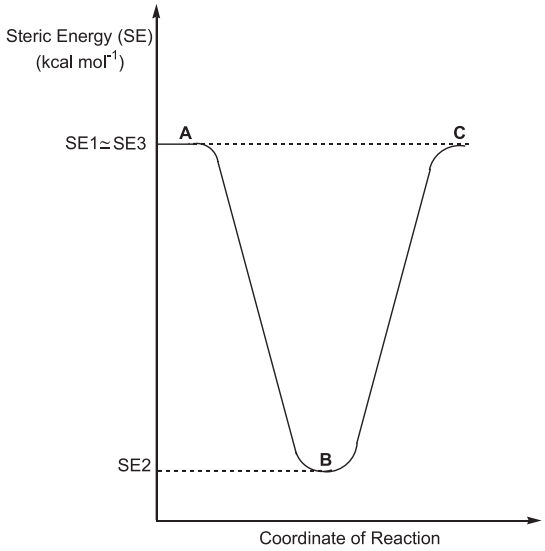


Figure S12. Qualitative graphic of steric energy (SE) versus coordinate of reaction for model **12**.

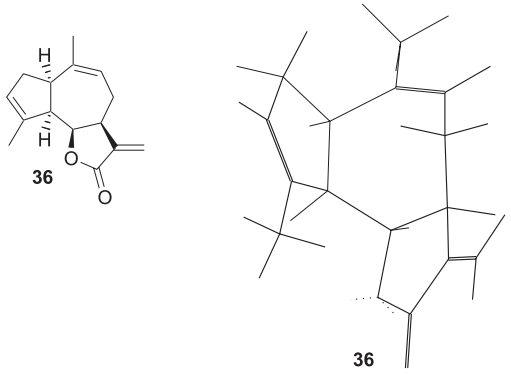


Figure S13. Three-dimensional structure of 6-*epi*-isoeremanthine (**36**).

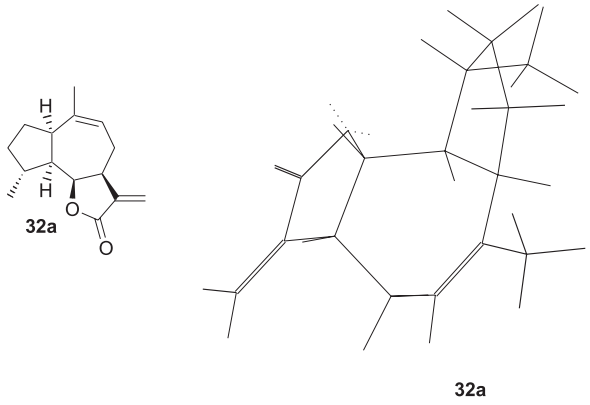


Figure S14. Three-dimensional structure of compound **32a**.

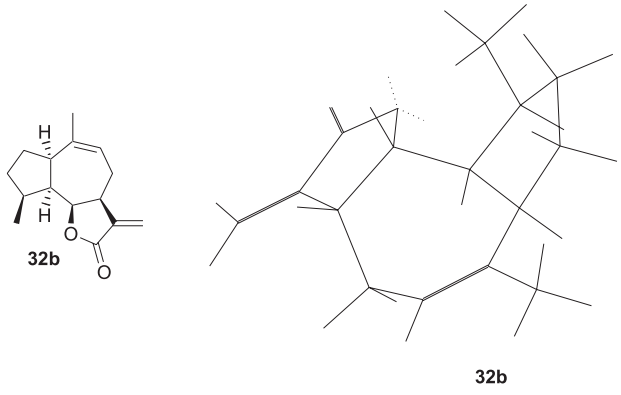


Figure S15. Three-dimensional structure of compound **32b**.