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

José C. F. Alves* and Edna C. Fantini†

Departamento de Química, Instituto de Ciências Exatas, Universidade Federal Rural do Rio de Janeiro, 23890-970 Seropédica-RJ, Brazil

As α-methylene-γ-lactonas 4(15)-dihydroeremanthine (8), 4(15),9(10)-tetrahydroeremanthine (9), isoeremanthine (10), acetato alílico Δ^{1,10} (11), 1(R),10(R)-diidromicheliolide (12) e 4α-hidróxi acetato alílico Δ^{1,10} (13) foram sintetizadas a partir do produto natural abundante eremanthine (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, Et3N, 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.

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 methenes. 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,9 in this paper we report the syntheses of 4(15)-dihydroeremanthine (8), 4(15),9(10)-tetrahydroeremanthine (9), isoeremanthine (10), allylic acetate Δ^{1,10} (11), 1(R),10(R)-diidromicheliolide (12) and 4α-hydroxy allylic acetate Δ^{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
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 pseudogaianolides.

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 that resulted in a high tension at the lactonic ring, evidenced through its infrared spectral data. 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. 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. For the synthesis of allylic acetate 11 we planned to obtain it through an elimination step of iodohydrins 18-19, previously described, by metal in acid medium to generate the respective products 16 and 11. 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, by the same procedure used in the conversion of 18 in 16, followed by stage of methanol elimination commonly used with eremanthine derivatives and subsequent acetylation of hydroxy group at C-9 position. Substance 12, previously synthesized from diol 21, would be obtained by the same procedures. Substance 13 would be obtained by simple reaction of methanol elimination accomplished on compound 21, previously described, 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, 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 1H 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 1H NMR.

For the synthesis of model 9 ii 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 1H NMR. The spectrum revealed that we obtained a mixture of 3 substances in a proportion of 2:5:3, measured by...
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 1H 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 1H 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
energies (Table 1), by using MM2 program, 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 1H 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, we used conditions v (Scheme 1). After the time of

| 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,\textsuperscript{15} we employed conditions vi–ix as outlined in Scheme 1. Epoxidation of eremanthine (1) with dilute 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.\textsuperscript{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 chromatography 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\textsubscript{3}N 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.\textsuperscript{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,\textsuperscript{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\textsubscript{7}) while substance 25 has the seven-membered ring in twist-boat conformation with a pseudo-C\textsubscript{2} axis passing through the C-8 position (TB\textsubscript{8}).\textsuperscript{9} Conformations of the seven-membered ring of substances 16 and 25, obtained in the MM2 program\textsuperscript{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)\textsuperscript{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\textsuperscript{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\textsuperscript{6,15}-cycloguaianes derived from eremanthine.\textsuperscript{11,14} The structure of substance 24 was confirmed by comparison of its \textsuperscript{1}H NMR, IR and R\textsubscript{f} data with the ones of this substance, previously obtained by opening of epoxide 9,10-\textsuperscript{α}-epoxy-eremanthine in acid medium, followed by a protection stage of \textsuperscript{α}-methylene-\textsuperscript{γ}-lactone with methanol and sodium carbonate.\textsuperscript{15} Moreover, analysing three-dimensional structures of compounds 24 and (24)-1-epi, obtained by MM2 program,\textsuperscript{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.](image-url)
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 1H 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 Rf. This mixture was submitted to 1H
Study of the Inversion Reaction of the Lactonic Fusion on Eremanthine Derivatives

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

| Hydrogens | δ (Multiplicity, J / Hz)
|-----------|-----------------
| H-15      | 5.11 (bs)       |
| H-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.

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). 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 Rf, in a proportion of 3:1, measured by integrals relative to the signals of C13-H of the two products at 1H NMR spectrum. Major product corresponded to diol 17 previously described 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 1H 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.
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 on 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 nucleophytic 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 nucleophytic displacement of mesylate leaving group.21 For the study of stereochemical inversion on alkoxy carbon of the lactones derived from eremanthine (I), 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 skeleton22 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 alkoxyphosphonium22 or by oxidation-reduction on C6-OH of an eremanthine derivative10,11 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 irreversible to generate intermediates as D.22 Soon
afterwards, the intramolecular nucleophilic substitution (SNi) should occur 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 hydrolyze 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 1H 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 1H NMR spectra of products with cis lactonic fusion is related 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
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.

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

| Exp. | Starting Materials | Reactions of opening of the lactonic ring | Reactions of lactonic fusion inversion |
|------|------------------|------------------------------------------|----------------------------------------|
|      | Time (min) | Product | Solvent | Products (%) - Proportion |
| 1    | 1440 | ![Image](image1.png) | THF | ![Image](image2.png) (92% - 1:1) |
| 2    | 1440 | ![Image](image3.png) | THF | ![Image](image4.png) (94% - 30:1) |
| 3    | 5 | ![Image](image5.png) | THF | ![Image](image6.png) (92% - 6:1) |
| 4    | 60 | ![Image](image7.png) | THF | Products of Polymerization and Decomposition |
| 11   | ![Image](image8.png) | ![Image](image9.png) | ![Image](image10.png) | ![Image](image11.png) (40% - 6:1) (4 products) |
| 5    | 5 | ![Image](image12.png) | THF | ![Image](image13.png) (89% - 3:1) |
| 6    | 10 | ![Image](image14.png) | DMSO | ![Image](image15.png) (72% - 5:3) |
| 7    | 10 | ![Image](image16.png) | THF | ![Image](image17.png) (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.
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. In Table 7 are depicted the torsion angles for these substances obtained in the MOPAC program. 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).

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 1H 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 1H 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 1H 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, -OCOCH3) and 5.09 (m, 1H, C9-H) - 1H 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
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$_3$CN) 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 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

| Exp. | Starting Materials and Products | H-6 $\delta$ (Multiplicity, J / Hz) | H-9 $\delta$ (Multiplicity, J / Hz) | H-13 $\delta$ (Multiplicity, J / Hz) | H-14 $\delta$ (Multiplicity, J / Hz) | H-15 $\delta$ (Multiplicity, J / Hz) |
|------|--------------------------------|------------------------------------|------------------------------------|------------------------------------|------------------------------------|------------------------------------|
| 1    | 8                              | 4.05 (m)                           | 5.55 - 5.35 (m)                    | 6.20 - 6.05 (m)                    | 1.78 (bs)                          | 1.13 (d, 6.4)                      |
|      |                                | 3.64 (m)                           |                                    |                                    |                                    |                                    |
| 9    | 4.17 (t, 10.5)                 |                                    | 6.18 (d, 3.6)                      | 6.15 (d, 3.3)                      | 0.97 (d, 7.2)                      | 1.17 (d, 6.4)                      |
|      | 4.02 (dd, 9.3 and 10.2)        |                                    |                                    |                                    | 0.95 (d, 6.2)                      |                                    |
|      | 3.81 (t, 9.9)                  |                                    |                                    |                                    |                                    |                                    |
| 2    | 34                             | 4.85 - 4.75 (m)                    |                                    |                                    |                                    |                                    |
| 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)                          |
| 4    | 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)                      |
| 5    | 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)                      |
| 6    | 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)                    |
| 7    | 12                             | 4.02 (t, 10.2)                     | -                                  | 6.13 (d, 3.5)                      | 5.41 (d, 3.2)                      | 0.96 (d, 7.2)                      |
|      |                                |                                    |                                    |                                    |                                    | 1.34 (s)                           |
| 8    | 40                             | 4.12 (d, 6.4)                      | -                                  | 6.24 (bs)                          | 5.64 (bs)                          |                                    |
| 9    | 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)                           |
| 10   | 27                             | 4.78 (bd, 5.4)                     | 4.24 (m)                           | 6.38 (bs)                          | 5.63 (bs)                          | -                                  |
| 11   | 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)                           |
| 12   | 28                             | 4.79 (bd, 5.6)                     | 5.09 (m)                           | 6.37 (bs)                          | 5.62 (bs)                          | -                                  |

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.

Scheme 7. Reagents and conditions: i) 4 mol L$^{-1}$ NaOH (5.5 equiv), CH$_3$CN (reflux - 5 h).
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. 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 stabler conformations in the substrates to conformers with higher steric energies at products with cis lactonic fusion, according to theoretical calculations obtained with MM2 program. 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 carboxylates to attack the C-6 positions of reactive intermediates containing the mesylate leaving groups, as well as 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

---

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

| Hydrogens | δ (Multiplicity, J / Hz) |
|-----------|--------------------------|
| H'-13'    | 6.47 (dd, 1.0 and 2.6)   |
| H'-13     | 5.56 (dd, 1.0 and 2.6)   |
| H-3       | 6.18 (d, 3.5)            |
| H-3'      | 5.21 (m)                 |
| H-9       | 4.88 (m)                 |
| H-9'      | 4.68 (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)                |

**Scheme 8.** Reagents and conditions: i) 4 mol L⁻¹ NaOH (5.5 equiv), CH₃CN (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 Diagramsa for the Seven-membered Rings | Products | Conformational Diagramsa for the Seven-membered Rings |
|--------------------|-------------------------------------------------------|----------|-------------------------------------------------------|
| ![Image](image1.png) | ![Image](image2.png) | ![Image](image3.png) | ![Image](image4.png) |
| ![Image](image5.png) | ![Image](image6.png) | ![Image](image7.png) | ![Image](image8.png) |
| ![Image](image9.png) | ![Image](image10.png) | ![Image](image11.png) | ![Image](image12.png) |
| ![Image](image13.png) | ![Image](image14.png) | ![Image](image15.png) | ![Image](image16.png) |
| ![Image](image17.png) | ![Image](image18.png) | ![Image](image19.png) | ![Image](image20.png) |
| ![Image](image21.png) | ![Image](image22.png) | ![Image](image23.png) | ![Image](image24.png) |
| ![Image](image25.png) | ![Image](image26.png) | ![Image](image27.png) | ![Image](image28.png) |
| ![Image](image29.png) | ![Image](image30.png) | ![Image](image31.png) | ![Image](image32.png) |
| ![Image](image33.png) | ![Image](image34.png) | ![Image](image35.png) | ![Image](image36.png) |

*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\textsubscript{2}-axis (C\textsubscript{2}), pseudo-C\textsubscript{2} axis (~C\textsubscript{2}), C\textsubscript{s} plane (C\textsubscript{s}) or pseudo-C\textsubscript{s} plane (~C\textsubscript{s})].
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 Rf, their correspondent allylic acetates 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 (1H: 200 MHz and 13C: 50.3 MHz) spectrometer. CDCl3 was used as the solvent and TMS as internal standard. Coupling constants (J) are reported in Hertz (Hz). Multiplicities are indicated as s (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 (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 F254 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(SO4)2 light (UV) and/or for contact of the plates with silica gel impregnated with iodine and/or spraying with 2% Ce(SO4)2. 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 minimum RMS gradient of 0.100 and displaying each iteration.16

**Table 7. 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      | 39.365      | -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      | -62.935      | 116.450      | -51.891      | -37.375     | 92.614      | -58.049     |
| 34c        | 16.200       | 42.914      | 51.823      | -34.707      | 63.367       | -97.105      | 54.622      | 22.119      | -68.249     |
| 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     | 93.719      | -67.002     |

(11S)-Guai-9-eno-4β(H)-13-methoxy-12,6α-lactone (22a) and (1S)-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 (1Hx1H-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 F254 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(SO4)2. 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 minimum RMS gradient of 0.100 and displaying each iteration.16
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) $\nu_{max}$ / cm$^{-1}$: 2920, 1780, 1660, 1450, 1380, 1320, 1180, 1100, 1000, 760. $^1$H NMR (CDCl$_3$, partial assignment): $\delta$ 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-4$\beta$(H),10$\beta$(H)-13-methoxy-12,6$\alpha$-lactone (23a); (11S)-Guaia-4$\beta$(H),10$\alpha$(H)-13-methoxy-12,6$\alpha$-lactone (23b) and (11S)-Guaia-4$\alpha$(H),10$\beta$(H)-13-methoxy-12,6$\alpha$-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) $\nu_{max}$ / cm$^{-1}$: 2920, 1775, 1460, 1180, 1100, 1000. $^1$H NMR (CDCl$_3$, partial assignment): $\delta$ 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 [6OH [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-4$\alpha$(H)-12,6$\alpha$-lactone (8a) and Guaia-9,11(13)-dieno-4$\beta$(H)-12,6$\alpha$-lactone (8b) (0.025 g, 71%) as a colourless oil. R$_f$ 0.70 (25% EtOAc / hexane).

$^1$H NMR (CDCl$_3$, partial assignment): $\delta$ 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-4$\beta$(H),10$\beta$(H)-12,6$\alpha$-lactone (9a); Guai-11(13)-eno-4$\beta$(H),10$\beta$(H)-12,6$\alpha$-lactone (9b) and Guai-11(13)-eno-4$\alpha$(H),10$\beta$(H)-12,6$\alpha$-lactone (9c) (0.030 g, 84%) as a colourless oil. R$_f$ 0.76 (50% EtOAc / hexane). IR (film) $\nu_{max}$ / cm$^{-1}$: 2920, 1760, 1460, 1260, 1150, 985. $^1$H NMR (CDCl$_3$, partial assignment): $\delta$ 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$_2$O (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$_2$SO$_4$, 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) $\nu_{max}$ / cm$^{-1}$: 3010, 2910, 1760, 1660, 1625, 1440, 1375, 1305, 1260, 1230, 1145, 990, 960, 940, 815, 750, 665. $^1$H NMR (CDCl$_3$, partial assignment): $\delta$ 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), 4.42 (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)]. 13C NMR (CDCl$_3$): $\delta$ 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$_3$), 27.85 (CH$_3$), 17.63 (CH$_3$).

Guai-11(13)-eno-4$\alpha$,15$\alpha$,9$\alpha$,10$\alpha$-diepoxy-12,6$\alpha$-lactone (15)

Preparation of peracetic acid solution. H$_2$O$_2$ (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. CHCl₃ (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 (I).** Eremanthine (I) (0.300 g, 1.302 mmol) was dissolved in a solution of Ac₂O / CHCl₃ (21 mL), prepared as described above. The resulting solution was kept in the dark, was vigorously stirred at room temperature for 96 h. The mixture was transferred to a separatory funnel and then washed with H₂O (1 × 30 mL), aqueous 5% NaHCO₃ (1 × 30 mL) and again with H₂O (1 × 30 mL). The organic layer was separated and the aqueous phases were extracted with CHCl₃ (3 × 35 mL). The organic extracts were dried with Na₂SO₄, filtered under activated charcoal and the solvent removed under reduced pressure to give diepoxide 15 as a colourless crystalline residue (0.270 g, 90%) as a brownish oil. Rf 0.16 (50% EtOAc / hexane); m. p. 119 - 120 °C (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 H₂O (1 × 30 mL) and again with H₂O (1 × 30 mL). The organic layer was separated and the aqueous phases were extracted with CHCl₃ (3 × 35 mL). The organic extracts were dried with Na₂SO₄, filtered and concentrated in vacuum. It was obtained as a colourless crystalline residue (0.274 g, 80%). Rf 0.30 mL) and then used in the epoxidation reaction.

**General procedure for preparation of allylic derivatives 11, 16 and 24.** To a bottom 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). H₂O (50 mL) was added and then concentrated in vacuum. The concentrated mixture was extracted with CHCl₃ (3 × 30 mL) and again with H₂O (1 × 30 mL). The organic layer was separated and organic layer was washed with aqueous 5% NaHCO₃ (1 × 20 mL) and H₂O (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 Na₂SO₄, filtered and concentrated in vacuum to give: Alloyle acetate 19 (0.155 g, 90%) as a brownish oil. Rf 0.50 (50% EtOAc / hexane). IR (film) ν max/cm⁻¹: 3500, 2940, 2915, 1760, 1730, 1440, 1375, 1240, 1140, 1040, 980, 960, 920, 820, 760, 735. ¹H NMR (CDCl₃, 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), 3.63 (dd, J 2.1 and 10.8 Hz, 1H, H-5), 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)]}. ¹³C NMR (CDCl₃): δ 168.32 (C=O), 138.13 (C), 134.47 (C), 130.80 (C), 120.09 (CH₂), 83.00 (CH), 81.03 (C), 72.21 (CH), 55.93 (CH), 41.66 (CH), 37.22 (CH₂), 33.03 (CH₂), 30.02 (CH₂), 22.78 (CH), 14.87 (CH).
EtOAc (1 × 50 mL). The aqueous phase was separated and the organic layer was washed with aqueous 5% NaHCO₃ (1 × 50 mL) and H₂O (1 × 50 mL). The organic layer was separated and aqueous phases were extracted with EtOAc (1 × 50 mL). The organic layers were dried with Na₂SO₄, filtered and concentrated in vacuum.

**Allylic alcohol 16** (0.085 g, 98%) as a yellowish oil. R₈ 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 (CDCl₃, partial assignment): δ 6.10 (d, J 3.3 Hz, 1H, H-13), 3.54 (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 10.9 Hz, 1H, H-5), 3.30 (m, 1H, H-7), 2.70 - 1.10 {10H [1.81 (d, J 1.1 Hz, H-14)]}.

**Allylic acetate 11** (0.100 g, 98%) as a colourless oil. R₈ 0.65 (50% EtOAc / hexane). IR (film) ν_max / cm⁻¹: 3490, 2940, 1770, 1740, 1660, 1445, 1370, 1240, 1135, 1020, 740. ¹H NMR (CDCl₃, partial assignment): δ 6.10 (d, J 3.3 Hz, 1H, H-13), 3.54 (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, -OCOCH₃), 1.82 (d, J 1.1 Hz, H-14)]}.

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. R₈ 0.25 (50% EtOAc / hexane). IR (film) ν_max / cm⁻¹: 3450, 2920, 1770, 1660, 1440, 1380, 1320, 1180, 1100, 910, 760. ¹H NMR (CDCl₃, 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, -OCH₃), 2.90 - 1.10 {10H [2.77 (m, J 7.7 Hz)]}.

**Allylic acetate 11** (0.062 g, 95%) as a colourless oil. R₈ 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 CHCl₃ and EtOAc to give: *Allylic acetate* 13 (0.038 g, 54%) as a colourless oil. Crystallization in CHCl₃ yielded 13 as colourless crystals. [m.p. 132 - 134 °C]. Rᵢ 0.37 (50% EtOAc / hexane). IR (film) ν_max / cm⁻¹: 3500, 2940, 1775, 1735, 1670, 1440, 1375, 1240, 1140, 990, 960, 820, 735. ¹H NMR (CDCl₃, 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, -OCOCH₃), 1.72 (bs, H-14), 1.27 (s, H-15)]}. ¹³C NMR (CDCl₃): δ 170.49 (C=O), 169.24 (C=O), 138.67 (C), 138.22 (C), 129.12 (C), 119.64 (CH₃), 83.50 (CH), 80.18 (C), 73.65 (CH), 57.84 (CH), 42.27 (CH), 37.85 (CH₃), 30.61 (CH₂), 22.59 (CH₃), 22.45 (CH₃), 21.21 (CH₃).

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 bottom 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. Et₃N (0.024 mL, 0.312 mmol) and MsCl (0.017 mL, 0.228 mmol). After the time of reaction, aqueous solution of 4% KOH (0.122 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 (0.218 mL, 0.90 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 neutralized with 10% (v/v) HCl until pH 3 and then extracted with EtOAc. It was obtained: crude product (0.015 g, 94%). ¹H NMR (CDCl₃): 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 Et₃N (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%).

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 Et₃N (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%). 1H NMR (CDCl3): 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 Et3N (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%).

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 Et3N (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%).

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 (0.27 mL) and it was added to resulting solution Et3N (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%).

1H NMR (CDCl3): partial assignment for the substance 27 (see Table 4).

Regeneration of α-methylene-γ-lactone by methanol elimination using CH3CN as the solvent

Eremanthine (1). A solution of eremanthine methoxy derivative (14) (0.021 g, 0.080 mmol) in CH3CN (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 H2O (2 × 20 mL). The organic layer was separated and aqueous phases were extracted with EtOAc (2 × 20 mL). The organic phases were dried with Na2SO4, filtered and concentrated in vacuum. It was obtained a brownish oil (0.017 g, 94%) characterized as eremanthine (1).

Lactonic fusion inversion of substance 12 (Exp. 1 - Table 3)

A solution of diol 21 (0.012 g, 0.040 mmol) in CH3CN (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 H2O (2 × 20 mL). The organic layer was separated and the aqueous phases were exhaustively extracted with EtOAc (3 × 20 mL). The organic phases were dried with Na2SO4, filtered and concentrated in vacuum. It was obtained a brownish oil (0.008 g, 73%) identified as a mixture of epimers 17 and 27. This material is available free of charge via the Internet at http://jbcs.sbq.org.br.

Acknowledgments

J. C. F. A. thanks CNPq for the fellowship, Dequim-UFRJRJ for running the NMR and IR spectra, NPPN-
UFRJ for the mass spectrum of allylic alcohol 16 and the referees as well as the JBCS editorial staff for helpful suggestions.

References

1. Fraga, B. M.; Nat. Prod. Rep. 2005, 22, 465; Ibid. 2006, 23, 943.
2. Vichnewski, W.; Gilbert, B.; Phytochem. 1972, 11, 2563; Baker, P. M.; Fortes, C. C.; Fortes, E. C.; Gazzinelli, G.; Gilbert, B.; Lopes, J. N. C.; Pellegrino. J.; Tomassini, T. C. B.; Vichnewski, W.; J. Pharm. Pharmacol. 1972, 24, 853; Corbella, A.; Gariboldi, P.; Jommi, G.; Ferrari, G.; Phytochem. 1974, 13, 459; Lima, P. D. B.; M.Sc. Dissertation, NPPN, Universidade Federal do Rio de Janeiro, Brazil, 1983.
3. Vajs, V.; Nevescanin, M.; Macura, S.; Juranic, N.; Menkovic, N.; Milosavljevic, S.; Fitoterapia 2003, 74, 508.
4. Goldsby, G.; Burke, B. A.; Phytochem. 1987, 26, 1059.
5. Money, T.; Wong, M. K. C.; Tetrahedron 1996, 52, 6307.
6. Kim, S. H.; Oh, S. M.; Kim, T. S.; Eur. J. Pharmacol. 2005, 511, 89.
7. Romo, J.; Joseph-Nathan, P.; Diaz, F. A.; Tetrahedron 1964, 20, 79.
8. Alves, J. C. F.; Fantini, E. C.; J. Braz. Chem. Soc. 2005, 16, 749.
9. For a survey on the conformational analysis of hydroazulenes see: Hendrickson, J. B.; Tetrahedron 1963, 19, 1387; De Clercq, P. J.; J. Org. Chem. 1981, 46, 667; De Clercq, P. J.; Tetrahedron 1981, 37, 4277.
10. Fantini, E. C.; Rabi, J. A.; Cienc. Cult. 1985, 37 (7 Supl.), 417.
11. Fantini, E. C.; PhD Thesis, Universidade Federal do Rio de Janeiro, Brazil, 1985.
12. Fantini, E. C.; Rabi, J. A.; Cienc. Cult. 1983, 35 (7 Supl.), 403.
13. Maçaira, L. A.; Garcia, M.; Rabi, J. A.; J. Org. Chem. 1977, 42, 4207.
14. Fantini, E. C.; Ferreira, J. L. P.; Rabi, J. A.; J. Chem. Res. (S), 1986, 298.
15. Fantini, E. C.; Rabi, J. A.; Cienc. Cult. 1986, 38 (7 Supl.), 521.
16. Cambridge Soft Corporation; CS Chem3D Ultra 7.0, Molecular Modeling and Analysis; Cambridge, 2001.
17. Ferreira, J. L. P.; M.Sc. Dissertation, NPPN, Universidade Federal do Rio de Janeiro, Brazil, 1985.
18. Alves, J. C. F.; M.Sc. Dissertation, Universidade Federal Rural do Rio de Janeiro, Brazil, 1993.
19. Boucheron, C.; Compain, P.; Martin, O. R.; Tetrahedron Lett. 2006, 47, 3081.
20. Krishna, P. R.; Reddy, P. V. N.; Tetrahedron Lett. 2006, 47, 4627.
21. Kocalka, P.; Pohl, R.; Rejman, D.; Rosenberg, I.; Tetrahedron 2006, 62, 5763.
22. Lansbury, P. T.; Vacca, J. P.; Tetrahedron Lett. 1982, 38, 2797.
23. Hendrickson, J. B.; J. Am. Chem. Soc. 1967, 89, 7047.
24. Fischer, N. H.; Wu-Shih, Y. F.; Chiari, G.; Fronczek, F. R.; Watkins, S. F.; J. Nat. Prod. 1981, 44, 104 and references cited therein.
25. Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R.; Purification of Laboratory Chemicals, 2nd ed.; Pergamon Press Ltd: New York, 1980.

Received: October 17, 2006
Web Release Date: May 21, 2007