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Review Article

A Review on the Chemistry of Eremanthine: A Sesquiterpene Lactone with Relevant Biological Activity

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The several aspects on the chemistry of eremanthine such as isolation, structural classification, biological activity, synthesis, and chemical transformations in other sesquiterpene lactones are described in this review. The main publications on this sesquiterpenolide, from its isolation of natural sources in 1972 to the current days, are included.

1. Introduction

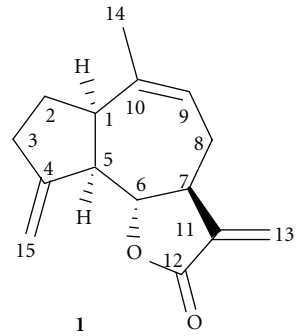
Eremanthine (**1**) (Figure 1) is a sesquiterpene lactone abundantly found in the Brazilian Compositae (*Asteracea*) *Eremanthus elaeagnus* [1] and *Vanillosmopsis erythropappa* [2] (*Eremanthus erythropappus*) [3]. This compound is a target for studies because of its biological properties, structural complexity due to the presence of a flexible seven-membered ring in its skeleton, as well as for the possibility to transform it in other potentially bioactive sesquiterpene lactones.

This review is composed by five items which include the isolation, structural classification, biological activity, synthesis, and chemical transformations of eremanthine. The main publications on this sesquiterpenolide from its isolation of natural sources in 1972 to the current days are described in the present review. Special attention is given to the synthetic studies that were developed aiming at the preparation of potentially bioactive sesquiterpene lactones.

2. Isolation of Eremanthine

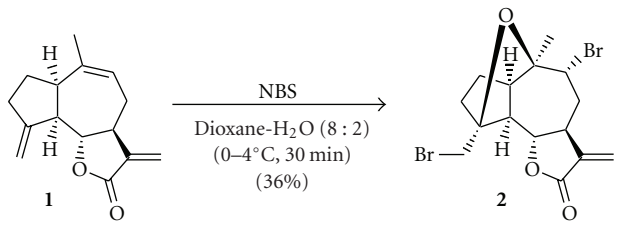
The search, here in Brazil, for plant-derived inhibitors against infections by cercariae of *Schistosoma mansoni* led to the isolation and characterization of eremanthine (**1**) from the oil of the Compositae *Eremanthus elaeagnus* and *Vanillosmopsis erythropappa* in 1972 [1, 2]. The extraction of crude oil from these vegetable species was made through the classic method of infusion of the pulverized trunk wood in organic solvent, at room temperature, followed by the evaporation stage of the extractor solvent under reduced pressure. Therefore, after evaporation of hexane that was used to extract the oil of *Eremanthus elaeagnus* and subsequent stage of crystallization of the crude oil with the same solvent, eremanthine (**1**) was obtained as colorless needles with melting point 73-74°C and $[\alpha]_D^{29} -59°$ (c 1.0 in $CHCl_3$) [1]. This value of specific optical rotation was later corrected as it is going to be described soon afterwards in this review. In the case of the hexane concentrated extract obtained from the extraction of the *Vanillosmopsis erythropappa* oil, eremanthine (**1**) was obtained after elution over column chromatography of silica gel [2]. The physical data of eremanthine obtained from *Vanillosmopsis erythropappa* were identical to the ones of eremanthine obtained from *Eremanthus elaeagnus*. The only structural feature not determined in those works published in 1972 was the absolute configuration at the carbon C-1.

It was demonstrated in 1974 that vanillosmin, isolated from *Vanillosmopsis erythropappa* by a research group in Italy [4], also had the same structure of eremanthine (**1**). In this case, the oil of that vegetable species was obtained from the acetone concentrated extract of the pulverized trunk wood in infusion, followed by the subsequent stages of treatment with a mixture of MeOH-H_2O and extraction with petroleum ether. The concentrated oil obtained after



1

Figure 1: Structure of eremanthine (**1**).



1 **2**

Scheme 1: Synthesis of the dibromoether **2**.

these stages was eluted over column chromatography of silica gel impregnated with $AgNO_3$ to furnish vanillosmin that was crystallized in hexane as long needles with melting point 62–62.5°C, boiling point 175–180°C/0.2 mm, and $[\alpha]_D^{20} -110°$. There were elucidated in that work the absolute configurations at C-1 and C-5 as being both *R*, on the basis of a series of chemical reactions.

The 1,5-*cis*-fused bicyclo[5.3.0]decane skeleton for **1** was confirmed by Garcia et al. [5] through the formation of dibromoether **2** when eremanthine (**1**) was treated with *N*-bromosuccinimide in dioxane containing 20% of water (Scheme 1). There was demonstrated through three-dimensional analysis of **1** that the formation of an ether linkage between the C-4 and C-10 positions was possible only if the five- and seven-membered rings were *cis*-fused. As the name eremanthine for **1** has historical precedence over vanillosmin the latter name passed no longer to be used. It was demonstrated in that work published by Rabi et al. [5] that the value of specific optical rotation previously calculated $[\alpha]_D^{29} -59°$ (c 1.0, $CHCl_3$) [1] was incorrect. A new determination was made and it was obtained $[\alpha]_D^{23} - 111.7°$ (c 1.0, $CHCl_3$) being, therefore, in agreement with the value of $[\alpha]_D^{20} -110°$ described in [4].

In 1985 Lima et al. [6] published a selective method for extraction of α-methylene-γ-lactones from *Vanillosmopsis erythropappa*. The oil of that vegetable species was obtained by the procedure of infusion of the pulverized trunk wood left in contact with hexane and then in ethanol. After evaporation of the extractor solvents, it was obtained an oil resultant from the hexane extract and another of the ethanol extract. The ethanolic extract furnished a dark oil that was exhaustively extracted with hexane to afford an oil. The aliquots of each oil were soon afterwards submitted to the separation procedure of α-methylene-γ-lactones from the other chemical substances of the crude extracts. Such procedure used the property of the unsaturated γ-lactones undergo facile 1,4-addition with nucleophilic substances. The sequence of reactions that was used to obtain eremanthine (**1**) for this procedure is outlined in Scheme 2. For this procedure the crude extract from *Vanillosmopsis erythropappa*, containing α-methylene-γ-lactones (**3**) in mixture with other substances, was dissolved in EtOAc and then submitted to reaction with aqueous solution of dimethylamine. The obtained mixture, containing the adducts of dimethylamine (**4**) together with other substances, was diluted with EtOAc and then washed with water. The separated and concentrated organic layer was submitted to reaction with acetic acid to furnish the acetates **5** in mixture with other substances. The acetates were extracted with water and the aqueous phase was washed with EtOAc, neutralized with saturated solution of sodium carbonate, and then reextracted with EtOAc. The mixture of the adducts of dimethylamine (**4**) was submitted, soon afterwards, to reaction with MeI to generate a mixture of iodides (**6**). Saturated solution of sodium carbonate was added and let to react at room temperature for 1 hour to the elimination reaction of the quaternary adducts of trimethylamine. There was obtained, after extraction of the last reaction, an exclusive mixture of α-methylene-γ-lactones (**3**). Filtration of this mixture of γ-lactones over column chromatography of silica gel, followed by crystallizations, furnished eremanthine (**1**) as majority product as well as the minority α-methylene-γ-lactones shown in Figure 2.

Due to the importance of bioactive chemical substances present in the crude extract from *Vanillosmopsis erythropappa* (*Eremanthus erythropappus*), tree popularly known by the name of *candeia*, nowadays a plan to conserve this forest species is being developed [7, 8]. The wood obtained in the forests of *candeia* is mainly sold for the industries of essential oils [9] that extract the crude oil through the steam distillation process. For that process, the pulverized trunk wood of *Eremanthus erythropappus* is put inside chemical reactors of high pressure and then it is heated at high temperature with water. The steam generated in the reactors passes, soon afterwards, for industrial condensers where it is cooled and then a mixture of oil and water is collected. The densest substance (water) is removed from the mixture to furnish the concentrated oil of *Eremanthus erythropappus* which is mainly sold for the industry of cosmetics that uses another important chemical substance found in that oil, the α-bisabolol (**20**) [10] (Figure 3). The use of the concentrated oil from *Eremanthus erythropappus*, extracted for the modern industrial method, certainly gives good results for isolation of eremanthine (**1**). Another recent method to extract the oil from *Eremanthus erythropappus*, using the supercritical extraction process and phase equilibrium of *candeia* oil with supercritical carbon dioxide, was reported by de Souza et al. [11].

2.1. Determination of the Absolute Stereochemistry of Eremanthine. The absolute stereochemistry of eremanthine (**1**) (vanillosmin) at the chiral carbons C-1, C-5, C-6, and C-7

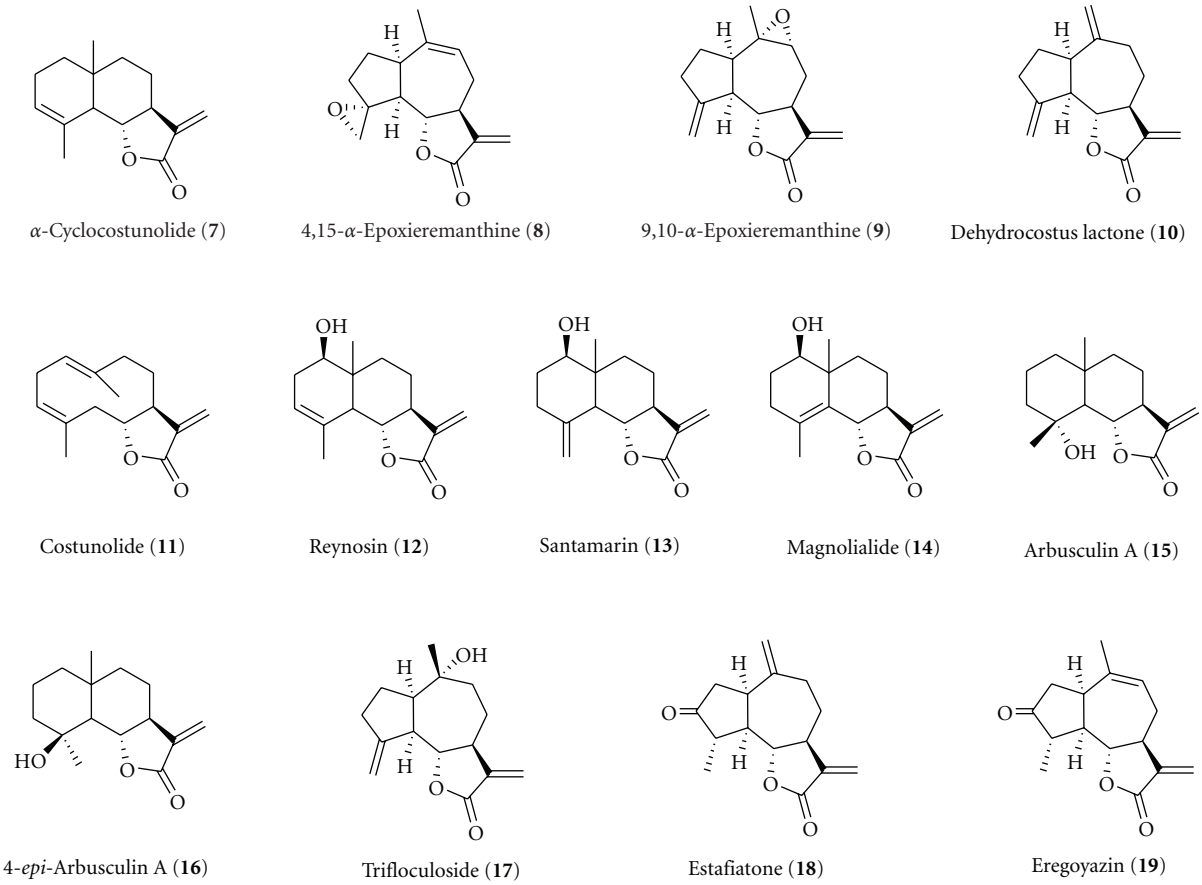


Figure 2: Minority α-methylene-γ-lactones isolated from *Vanillosmopsis erythropappa*.

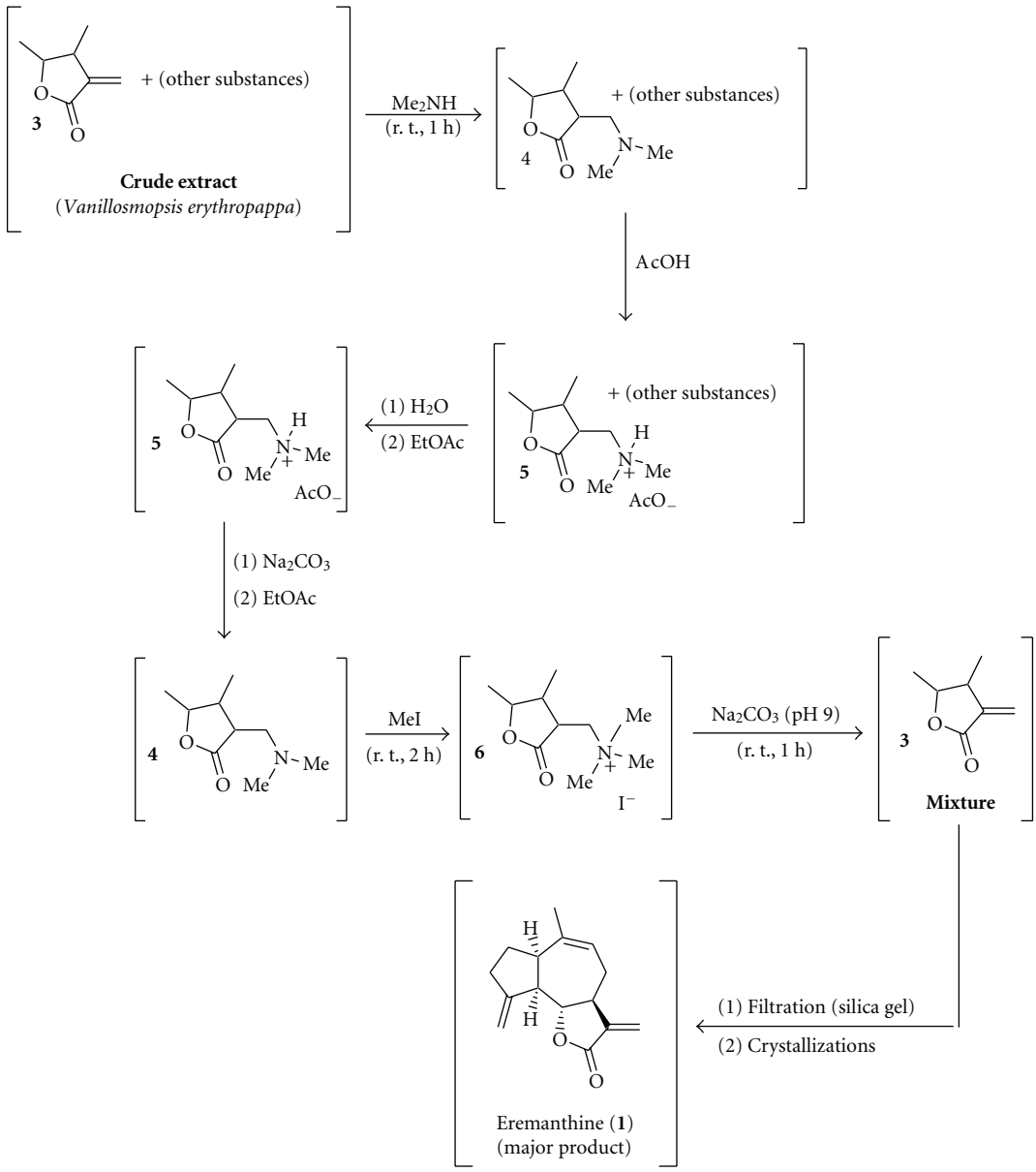
was determined through the correlation of derivatives from the substance **1** with other lactones that possess known absolute stereochemistry in these positions. The sequences of reactions that were employed by Corbella et al. [4] to synthesize the substances used to determine the absolute stereochemistry of eremanthine are outlined in Schemes 3–8.

As the most guaianolides possess *cis* fusion in the five- and seven-membered rings at the hydroazulene system, there was initially attributed the stereochemistry of eremanthine in those centers as shown in the chemical structure **1**. Reaction of substance **1** with $NaBH_4$ generated a single product characterized as the lactone **21** (Scheme 3). Reduction of this substance with hydrogen and soluble Wilkinson's catalyst furnished a product identified as the compound **22**. Hydrogenation of **22** in EtOAc with H_2 and Pd resulted in isomerization of the double bond C9-C10 to the tetra-substituted position C1–C10 to afford the compound **23** as the main product of that reaction. In the following stage, the compound **23** was synthesized starting from *O*-acetyl-isophoto-α-santonic lactone (**24**) (Scheme 4).

Catalytic hydrogenation of lactone **24** furnished the compound **25** of known absolute stereochemistry. Reaction of substance **25** with 1,2-ethanedithiol and $BF_3 \cdot OEt_2$furnished thioacetal **26**, resultant from the protection of carbonyl group at C-3 position and elimination of acetic acid. Reductive removal of the thioacetal **26** with Raney-Nickel generated a compound identified as the substance **23**, previously obtained from eremanthine (**1**).

To ensure that the acid treatment of the lactone **25** (Scheme 4) did not affect the configuration of the methyl at C-4, that is more stable in the *alpha* position than in the *beta* position, the C-4 epimer of compound **23** was prepared as described in Scheme 5. Alkaline treatment of the lactone **25** generated the compound **27** resultant from the hydrolysis of the acetate and epimerization at C-4 position. Thioacetalization of compound **27** furnished two products: one of them, the compound **28**, stayed with the hydroxy group at C-10 and the other, the compound **29**, resultant from elimination of water. Desulphurization of the thioacetal **29** generated the lactone **30**, whose physical data were different from those of the lactone **23** obtained from eremanthine (**1**) (Scheme 3). This correlation confirmed the structure proposed for the compound **23** and established the absolute configuration at C-5, C-6, and C-7 positions of eremanthine as shown in the chemical structure **1**.

To determine the absolute stereochemistry at C-1 position of eremanthine (**1**), the reactions outlined in Schemes 6–8 were performed. Starting from tetrahydroeremanthine (**22**), obtained from eremanthine (**1**) (Scheme 3), the oxymercuration-desmercuration reaction shown in



Scheme 2: Sequence of reactions used for the selective isolation of α-methylene-γ-lactones from *Vanillosmopsis erythropappa*.

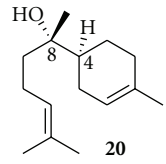
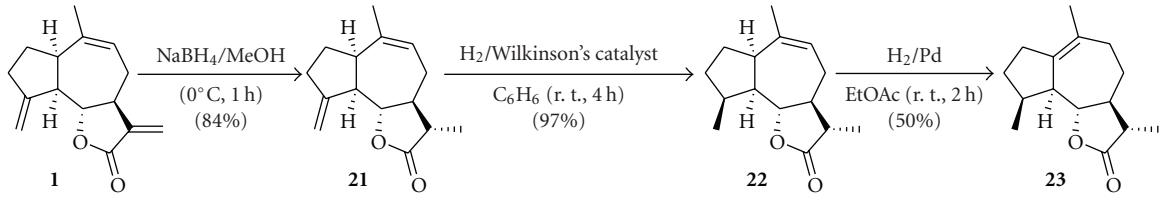


Figure 3: Structure of (-)-α-bisabolol (**20**).

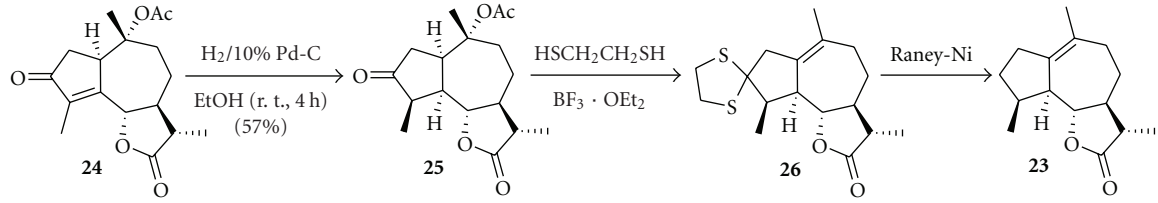
Scheme 6 was performed and two isomeric hydroxy-lactones **31** and **32** were obtained in the proportion of (1 : 12). The chemical structure of the substance **31** was confirmed through the synthesis depicted in Scheme 7.

Alkaline hydrolysis of the acetate **24** generated the lactone **33** (Scheme 7) that was submitted to catalytic hydrogenation to furnish the dihydroderivative **34**. Treatment of this compound with etanedithiol and $BF_3 \cdot OEt_2$, at low temperature, generated the thioacetal **35**. This compound was reduced with Raney-Nickel to afford a product whose physical data were identical to those of the hydroxylactone **31** derived from tetrahydroeremanthine (**22**).

The most abundant product of the oxymercuration-desmercuration reaction on tetrahydroeremanthine (**22**) was the hydroxy-lactone **32** (Scheme 6), which is the C-10 epimer of substance **31**. To ensure that the configuration at C-10 was the only difference between the structures **31** and **32**, the product **31** obtained from the conditions described in Scheme 7 was submitted to dehydration with thionyl chloride and pyridine at low temperature (Scheme 8). The anhydroderivative **36** obtained in that reaction was



Scheme 3: Synthesis of the lactone **23** starting from eremanthine (**1**).



Scheme 4: Synthesis of the lactone **23** starting from *O*-acetyl-isophoto-α-santonic lactone (**24**).

submitted to subsequent stage of oxymercuration-desmercuration to furnish a compound identical in all its physicochemical properties to the hydroxy-lactone **32**. These results demonstrated that the hydrogen at C-1 position of eremanthine (**1**) has *alpha* configuration and, consequently, the absolute stereochemistry of this substance is in agreement with the chemical structure shown in Figure 1.

The absolute configuration of eremanthine (**1**) was also confirmed in an article published in 1999 by Yuuya et al. [12]. In that publication the guaianolide **1** was synthesized starting from the natural product α-santonin.

3. Structural Classification of Eremanthine

Eremanthine (**1**) belongs to the class of substances denominated guaianolides. These substances possess the basic skeleton of bicyclo[5.3.0]decane, characteristic of the guaiane sesquiterpenes, to which was inserted at positions C-6 and C-7 or C-7 and C-8 a γ-lactonic ring (Figure 4).

3.1. The Biogenesis of Sesquiterpene Lactones. Guaianolides are biogenetically derived from the farnesyl pyrophosphate (**37**) that passed by cyclization to generate the cyclodecadiene **38**. This intermediate undergoes enzymatic oxydations to yield the germacranolide (**39**), a presumed precursor of the skeleton of guaianolides (Scheme 9) [13]. A detailed study on the biogenesis of sesquiterpene lactones was reported by Fischer et al. [14].

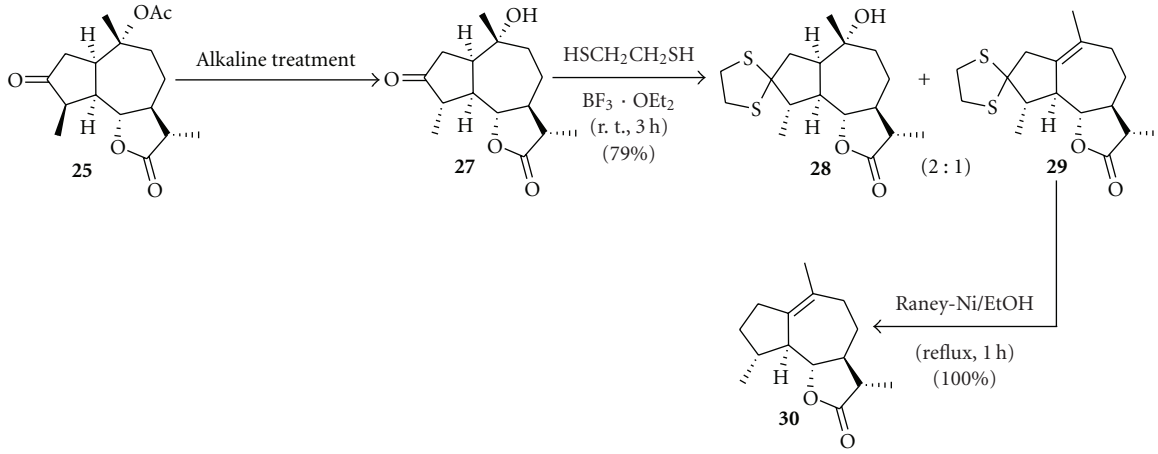
The skeletons of sesquiterpene lactones, with lactonic fusion at C-6 and C-7 positions, derived from germacranolides and the respective references were described in the works of Ferreira's *M.S.* [15] and Fantini's *Ph.D.* [16]. In Scheme 10 are outlined such biogenetical relationships reported in those works.

The biogenetical hypothesis of the guaianolides formation and their transformation into pseudoguaianolides reported by Fischer et al. [14] is outlined in Schemes 11–14. It was formulated that the skeleton of guaianolides is formed by the cyclization of a germacranolide-4,5-epoxide (**40**) in a chair-like transition state (Scheme 11). The intermediate *cis*-fused guaianolide cation (**41**) undergoes reaction with water to furnish the guaianolide **42** with *cis* fusion between the five- and seven-membered rings that is, with rare exceptions, the stereochemistry found in the most guaianolides.

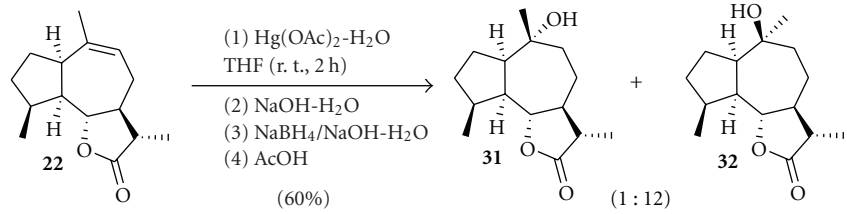
The biogenesis for the few *trans*-fused guaianolides found as natural products was proposed to proceed via either the melampolide-4,5-epoxide (**43**) or germacranolide-4,5-epoxide (**44**) pathways (Scheme 12). The cyclization of these compounds should furnish the *trans*-fused guaianolide cation (**45**) which after reaction with water would result in the formation of the skeleton **46** with *trans* fusion between the five- and seven-membered rings.

The biogenesis for the pseudoguaianolides-denominated ambrosanolides, with C-10β methyl group and lactonic ring at C-6 and C-7 positions with the C-6 oxygen at β orientation, is outlined in Scheme 13. The cyclization of the germacranolide-4,5-epoxide (**47**) would give the cation guaianolide (**48**) which upon double hydride and methyl shift, as indicated by the arrows, gives the ambrosanolide skeleton (**49**). As all ambrosanolides possess *cis* lactonic fusion at C-6 and C-7 positions, it was proposed that a C-6-β-oxygen would be assisting the rearrangement step of the carbocation **48** to compound **49**. The intramolecular frontside stabilization of the cationic center at C-10 by the C-6 oxygen at β position would allow a C-1 to C-10 hydride shift to occur before the competing step of elimination or nucleophilic attack at C-10 to form a guaianolide.

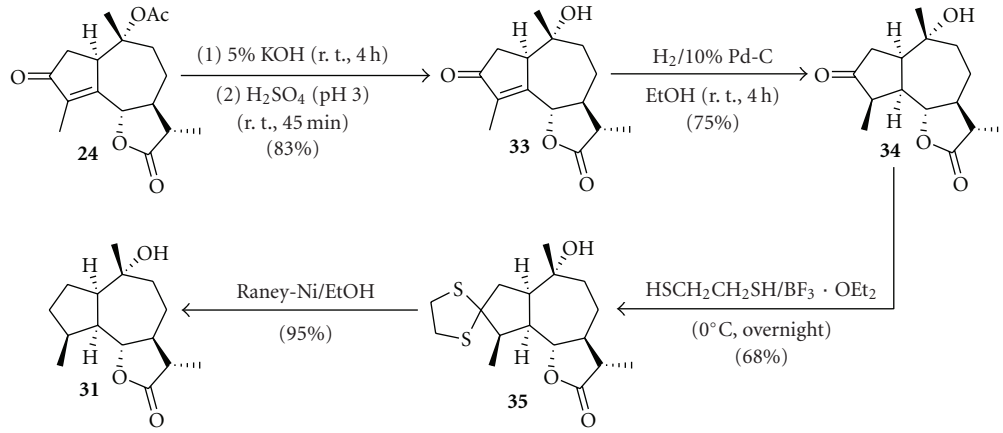
The biogenesis of the pseudoguaianolides-denominated helenanolides, with C-10α methyl group and lactonic ring at



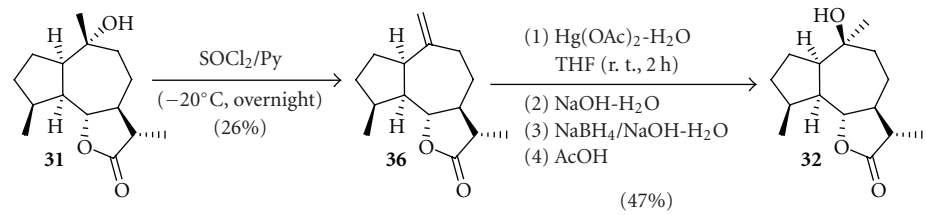
Scheme 5: Synthesis of the lactone **30**.



Scheme 6: Oxymercuration-desmercuration reaction performed on tetrahydroeremanthine (**22**).



Scheme 7: Synthesis of the compound **31** starting from the lactone **24**.



Scheme 8: Epimerization at C-10 position of the lactone **31**.

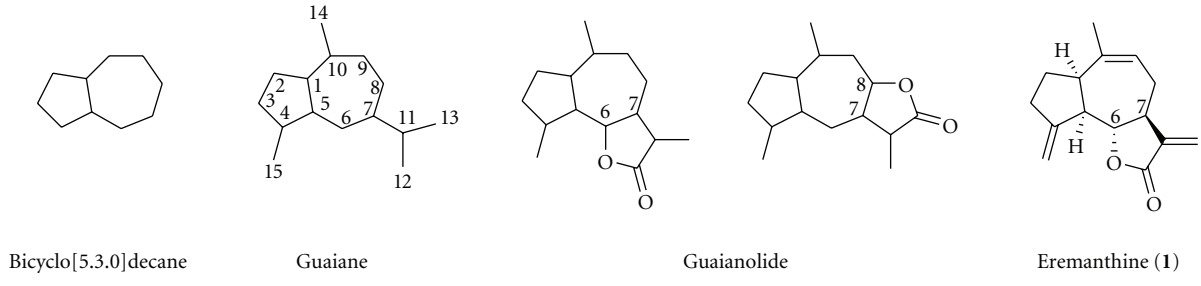
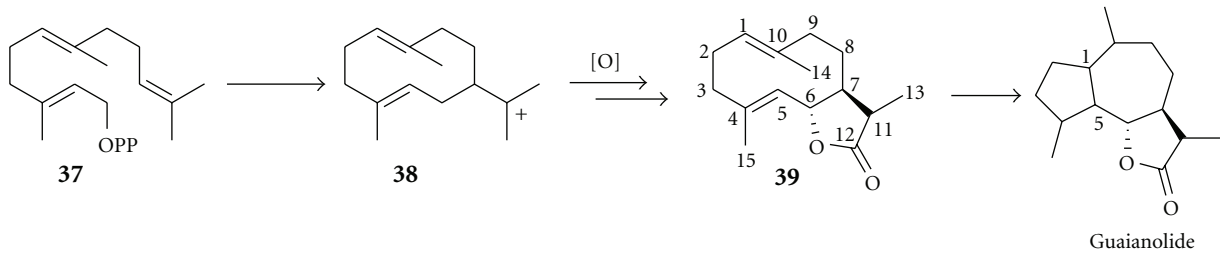


Figure 4: Bicyclo[5.3.0]decane, guaiane, guaianolide and eremanthine (**1**).



Scheme 9: Biosynthesis of guaianolides.

C-7 and C-8 positions with the C-8 oxygen oriented either α or β, is outlined in Scheme 14. Acid-induced cyclization of the melampolide-4,5-epoxide (**43**) would give the cation **45** from which by the indicated shifts, the skeleton of the helenanolides (**50**) would be formed. An alternative route to the helenanolide intermediate (**45**) could involve a germacranolide 4,5-epoxide precursor (**44**) which would provide the same cyclised skeleton (**50**) which is formed via the melampolide route.

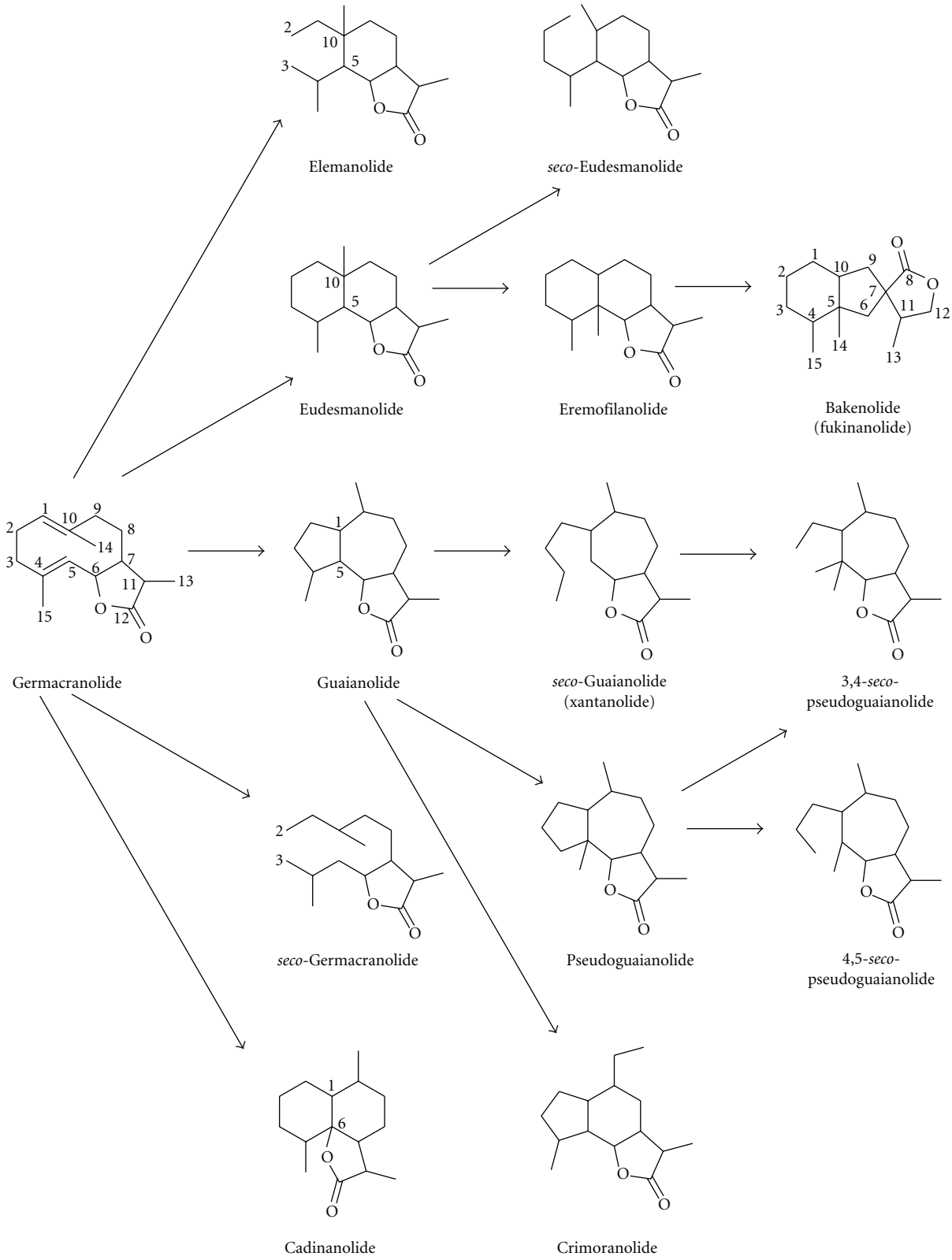
In 1981 Fischer et al. [17] published an article on the biomimetic transformation of guaianolide into pseudoguaianolide. The conditions studied in that biogenetic type *in vitro* conversion are outlined in Scheme 15. The reaction of epoxide **51** with $BF_3 \cdot OEt_2$ furnished the compounds **52** and **53** and not the desired product **54** with pseudoguaianolide skeleton. It was proposed that the minor product (**52**) resulted from the acid-catalysed opening of the ring epoxide of **51** and the major eudesmanolide **53** from the skeleton rearrangement of that substrate catalysed by $BF_3 \cdot OEt_2$. The nonformation of substance **54** starting from the epoxide **51** reinforces the hypothesis that, to occur the rearrangements indicated by the arrows in Scheme 15, there is necessary a precursor guaianolide with a β-oxygenated function at C-6 position.

Other articles related to biomimetic transformation of guaianolide into pseudoguaianolide were reported in literature [18–20]. The study on the biomimetic transformation of eremanthine is going to be discussed in this text at the section on chemical transformations of this natural product.

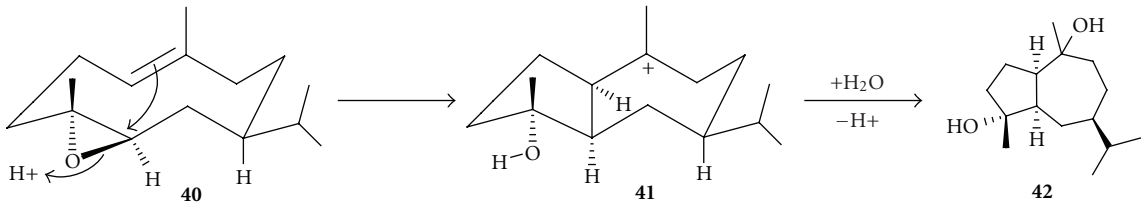
3.2. Stereochemistry of Bicyclo[5.3.0]Decane. The bicyclo [5.3.0]decane (hydroazulene system) is a nucleus present in a great variety of natural products such as the guaiane and pseudoguaiane sesquiterpenoids [21] and the guaiane [22–51], ingenane [52–67], daphnane [68–86], and asebotoxin [87–95] diterpenoids (Figure 5). Due to the chemical, biogenetical, and pharmacological interests that these classes of substances present, the literature reports a vast number of published works, with prominence for the reviews on sesquiterpenoids [21] and diterpenoids [96–101]. As eremanthine (**1**) belongs to the class of guaiane sesquiterpenoids (guaianolides), soon afterwards some considerations are going to be done on the stereochemistry of hydroazulene system present in its molecular structure.

The hydroazulene system is composed by a five-membered ring (rigid system) fused with a seven-membered ring (flexible system). Due to the flexibility of the seven-membered ring at the hydroazulene system, the study of conformational analysis of that system became necessary for a better understanding of stereoelectronic course of the reactions occured with the classes of substances that contain this nucleus in its hydrocarbon skeleton. The conformational analysis of hydroazulenes is also important for the interpretation of spectral data from nuclear magnetic resonance (NMR) of the substances that possess this system.

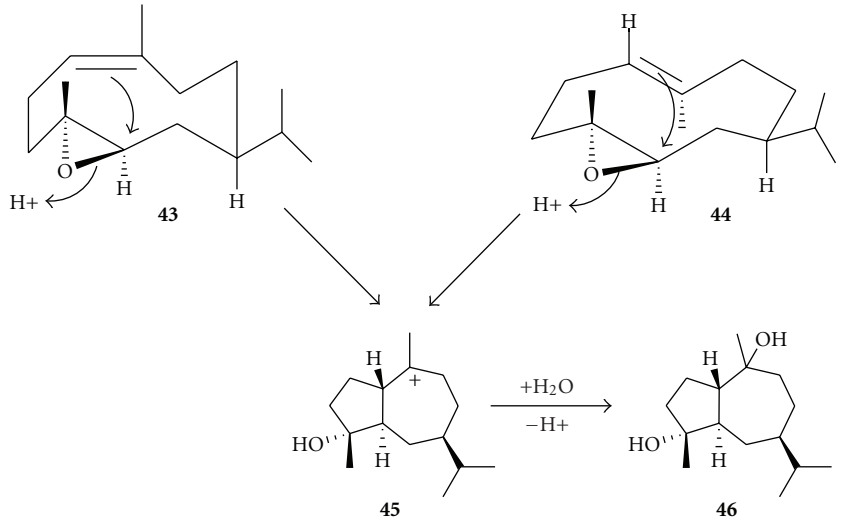
The study of conformational analysis applied to cyclic systems, including the hydroazulene, was initiated in the decade of 1960 with Hendrickson's works [102–109]. Subsequent studies, in that area, were published in the decade



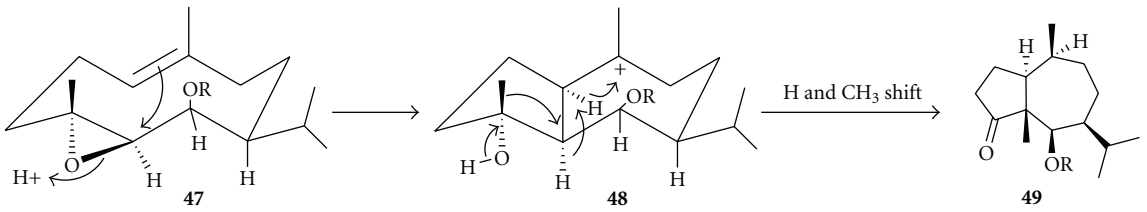
Scheme 10: Biogenesis of sesquiterpene lactones.



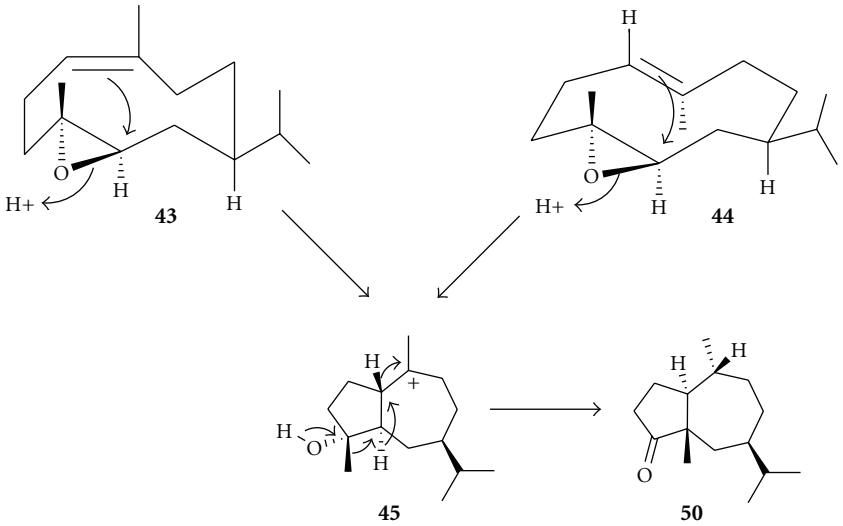
Scheme 11: Biogenesis of *cis*-fused guaianolides.



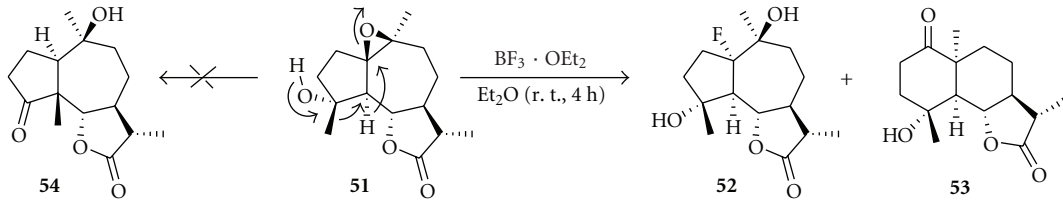
Scheme 12: Biogenesis of *trans*-fused guaianolides.



Scheme 13: Biogenesis of ambrosanolides.



Scheme 14: Biogenesis of helenanolides.



Scheme 15: Attempt of biogenetic *in vitro* conversion of the guaianolide **51** into pseudoguaianolide **54**.

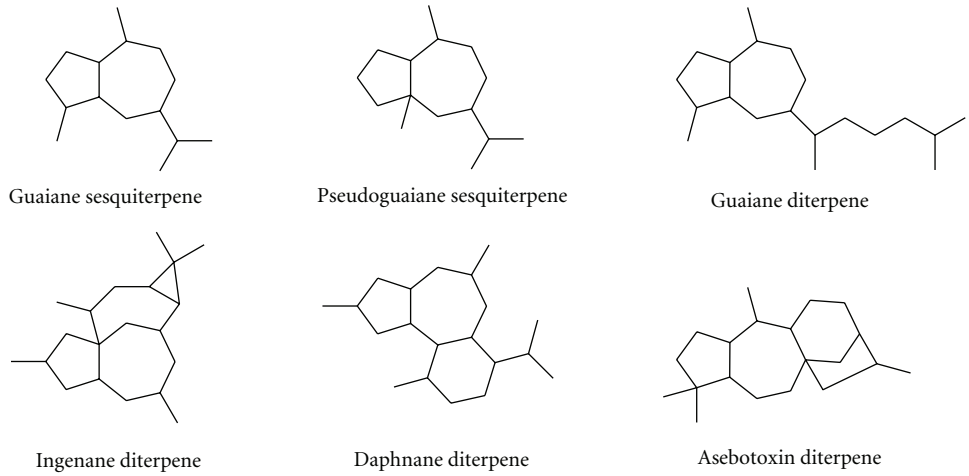


Figure 5: Hydrocarbon skeletons of guaiane and pseudoguaiane sesquiterpenes and guaiane, ingenane, daphnane and asebotoxin diterpenes.

of 1980 by Clercq [110–115]. Those works were focused on the conformational analysis of the seven-membered ring that commands the geometry of the hydroazulene system. According to the results of those published studies, the seven-membered ring can present itself in the basic conformations shown in Figures 6-7.

In Figure 6 the subscript used to define a particular form (twist-chair TC, chair C, twist-boat TB, and boat B) indicates the atom sectioned by the symmetry element and the strain energies are given in parenthesis in kilojoules per mol. The same annotation was used in Figure 7, with the symbol $\sim C_2$ indicating a pseudo-C_2 axis of symmetry.

According to Clercq [110] the chair and boat conformations of cycloheptane are flexible and undergo pseudorotation. The twist forms (TC and TB) with C_2-axis of symmetry are generally more stable than the chair (C) and boat (B) forms with a C_S plan of symmetry. In the case of cycloheptene, the chair form is generally the most stable conformation and the order of relative stability of conformers is the following: $C > \mathrm{TB}(C_2) > \mathrm{TB}\ (\sim C_2) > \mathrm{B}$. The method of de Clercq [110, 111], for systematic conformational analysis of hydroazulenes, was used in synthetic studies to explain the stereoselectivity of the reactions of sesquiterpene lactones that possess the hydroazulene skeleton in its molecular structure [115].

Nowadays, with the technological progresses, several research groups are using computation programs that were developed to aid in the visualization of the three-dimensional chemical structures of the molecules and to calculate their physical properties. It is possible to perform the conformational analyses of the studied substances, starting from the three-dimensional structures drawn by computation programs. Articles were published on the several modern techniques used to determine the conformations of the hydroazulene system from sesquiterpene lactones, including the analyses of X-ray diffraction, calculations of quantum mechanics, and molecular mechanics in combination with the NMR data [116–123].

4. Biological Activity of Eremanthine

Researchers verified that animals of laboratory (mice) were protected against infections caused by cercariae of *Schistosoma mansoni*, when the essential oils from *Eremanthus elaeagnus* and *Vanillosmopsis erythropappa* were applied on the skin of those guinea-pigs. That protective action was mainly attributed to the substance eremanthine (**1**), an abundant component found in those oils [1, 2]. The biological activity of eremanthine was attributed to the presence of an α-methylene-γ-lactone in its molecular structure [1]. That functional group was indicated as the main responsible for the biological activity in sesquiterpene lactones, due to its ability to react with the biological nucleophiles in a conjugate fashion [124–130]. The pharmacological results from the protective action of *Eremanthus elaeagnus* and *Vanillosmopsis erythropappa* oils were reported by Baker et al. [2].

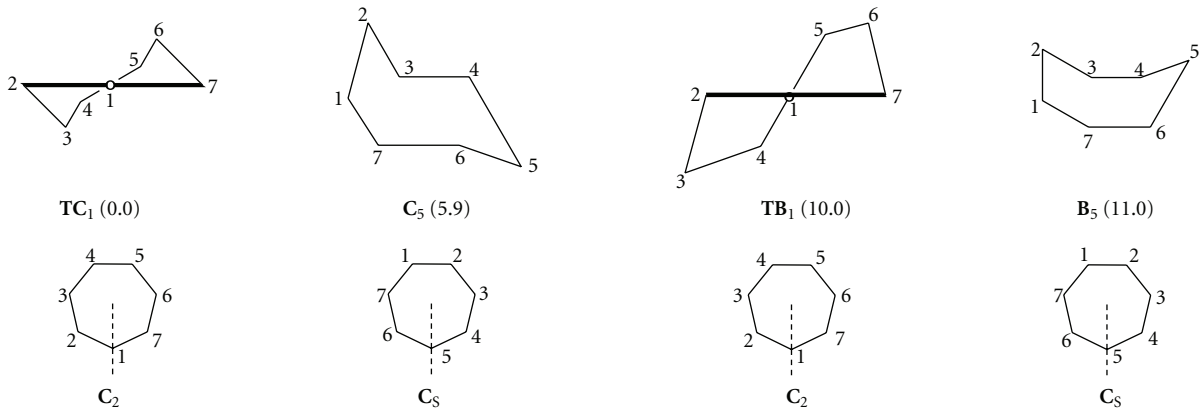


Figure 6: Conformational diagrams of the basic cycloheptane forms.

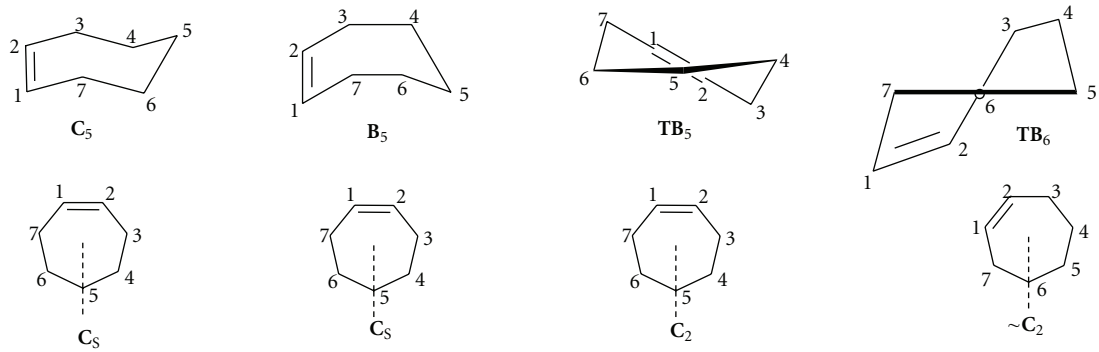
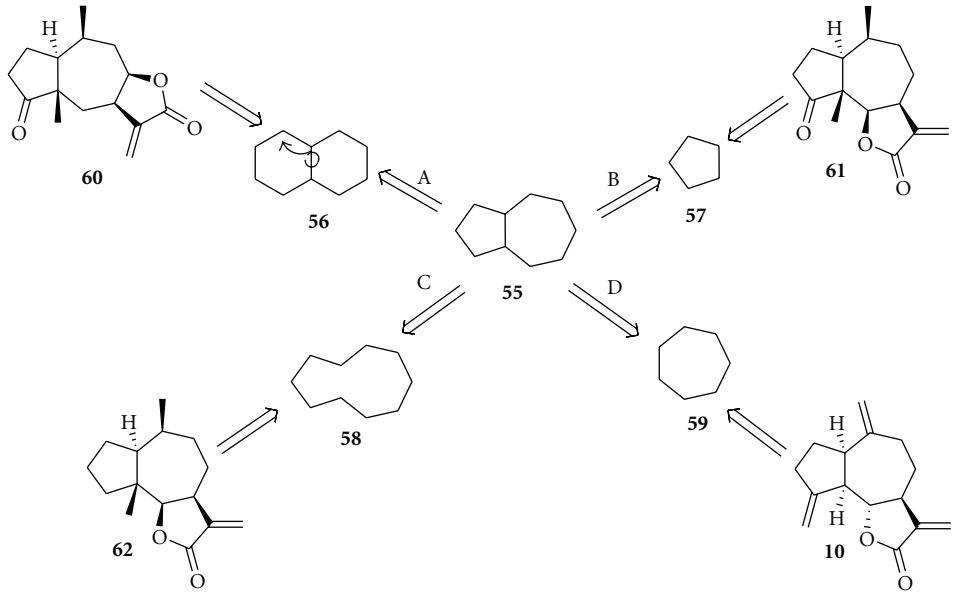
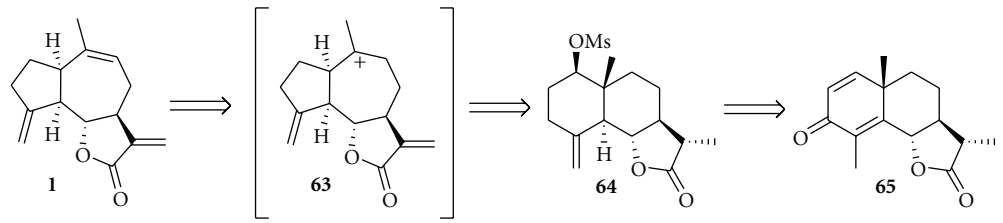


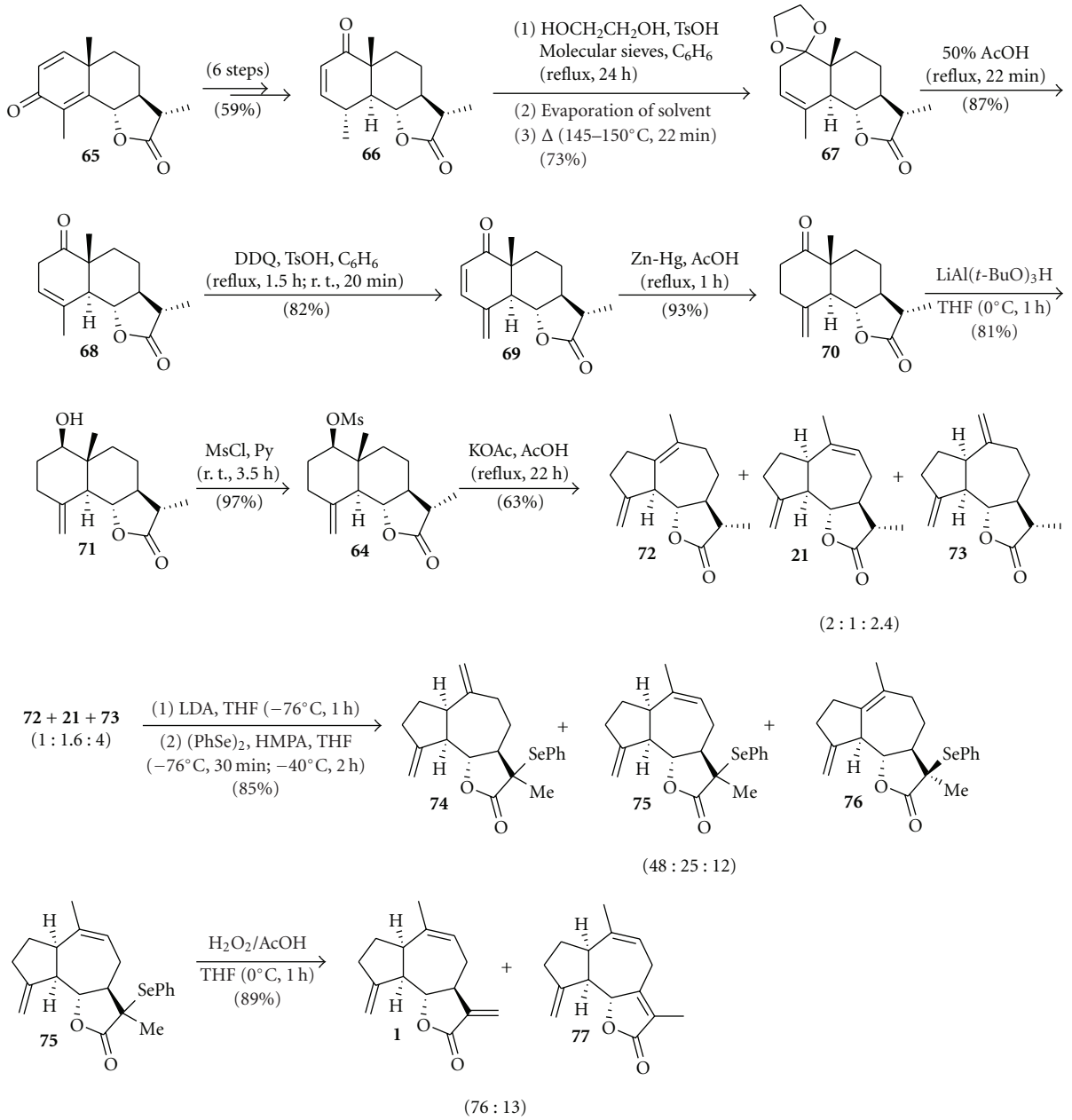
Figure 7: Conformational diagrams of the basic cycloheptene forms.



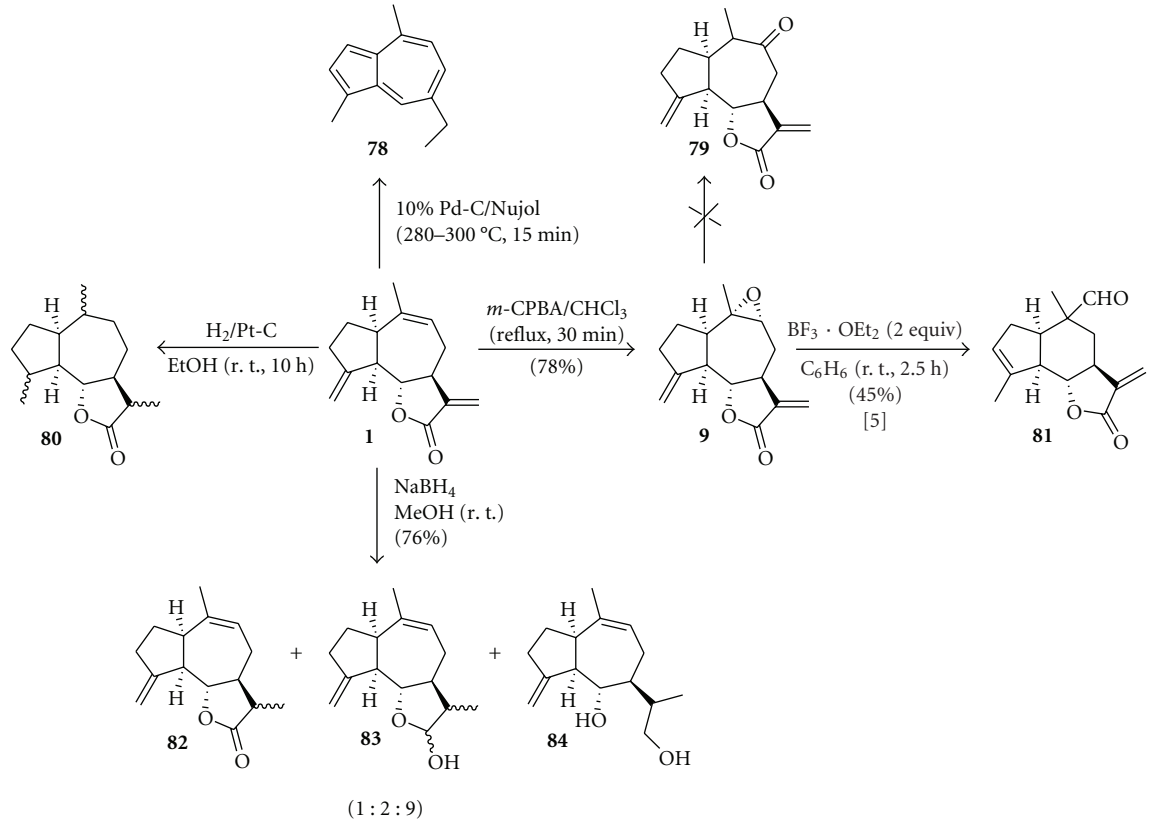
Scheme 16: Basic strategies to construction of the hydroazulene skeleton.



Scheme 17: Retroanalysis to the synthesis of eremanthine (**1**).



Scheme 18: Synthesis of eremanthine (**1**).



Scheme 19: The first chemical transformations of eremanthine (**1**).

5. Synthesis of Eremanthine

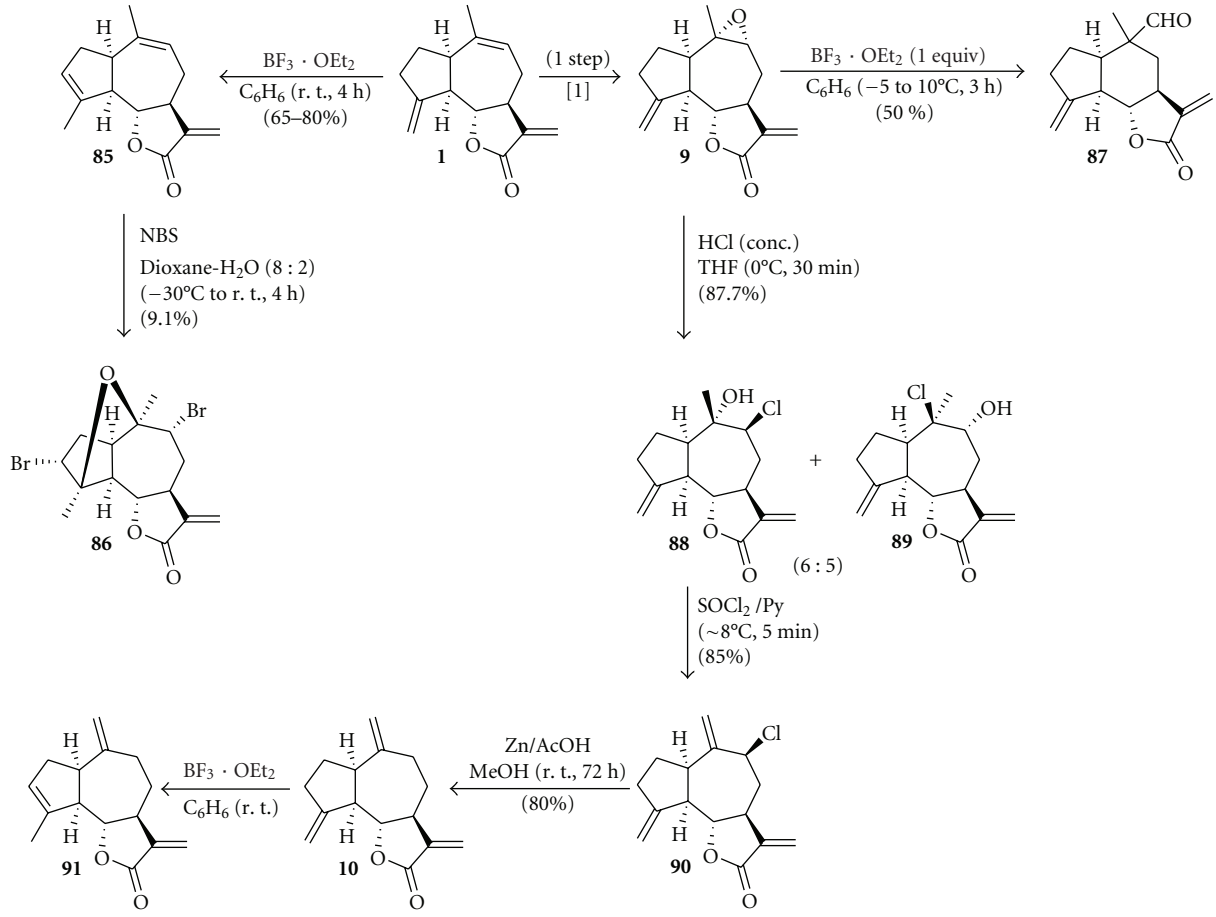
The synthesis of sesquiterpene lactones with their varied skeletons is composed by two crucial stages, which are the construction of the basic skeleton and the formation of the α-methylene-γ-lactone. In the following subitems some considerations are done about the construction of the hydroazulene skeleton characteristic of the guaiane [131] and pseudoguaiane sesquiterpenoids, the formation of the α-methylene-γ-lactone, besides the strategy and stages of the synthesis of eremanthine (**1**).

5.1. Basic Strategies to Construction of the Hydroazule Skeleton. The construction of the hydroazulene skeleton, reported by Heathcock et al. [132], involves four basic strategies which are shown in Scheme 16 with the respective substances that were synthesized.

The synthesis of confertin (**60**) [133] was accomplished by the strategy **A**, in which the construction of the hydroazulene skeleton (**55**) was planned starting from a hydronaphthalene precursor (**56**) through a rearrangement reaction. The damsim (**61**) [134] could be obtained by the strategy **B**, whose construction of the hydroazulene skeleton was planned starting from a cyclopentane precursor (**57**) on which the cycloheptane ring was inserted. In the synthesis of deoxydamsim (**62**) [135] the construction of the hydroazulene skeleton was planned by the strategy **C**, using a precursor derived from the cyclodecane (**58**), through a transannular rearrangement reaction. Finally in strategy **D**, used to the synthesis of dehydrocostus lactone (**10**) [136], the construction of the hydroazulene skeleton was planned starting from a cycloheptane derivative (**59**) on which the cyclopentane ring was inserted. The most recent literature on the synthesis of sesquiterpenoids reports the preparation of a chiron derived from cycloheptenone as a building block to the synthesis of guaiane sesquiterpene natural products [137] as well as the synthetic approaches to bicyclo[5.3.0]decane sesquiterpenes [138].

5.2. Synthesis of the α-Methylene-γ-Lactone Moiety. The α-methylene-γ-lactone is an important structural subunit found in several natural products with relevant biological activity. Due to the importance of this functional group, several researchers dedicated to the study of this structural moiety, with prominence to the various synthetic methods reported in literature [139–143].

5.3. Strategy to the Synthesis of Eremanthine. The enantioselective synthesis of eremanthine (**1**), developed by Yuuya et al. [12], employs the *chiron approach* strategy with the use of a chiral natural product as starting material on which chemical transformations are performed to reach the synthesis of the target molecule. There was used the strategy **A** shown in Scheme 16 to the construction of the hydroazulene skeleton of eremanthine (**1**), whose retrosynthetic analysis is presented in Scheme 17. In this strategy, the compound **1**



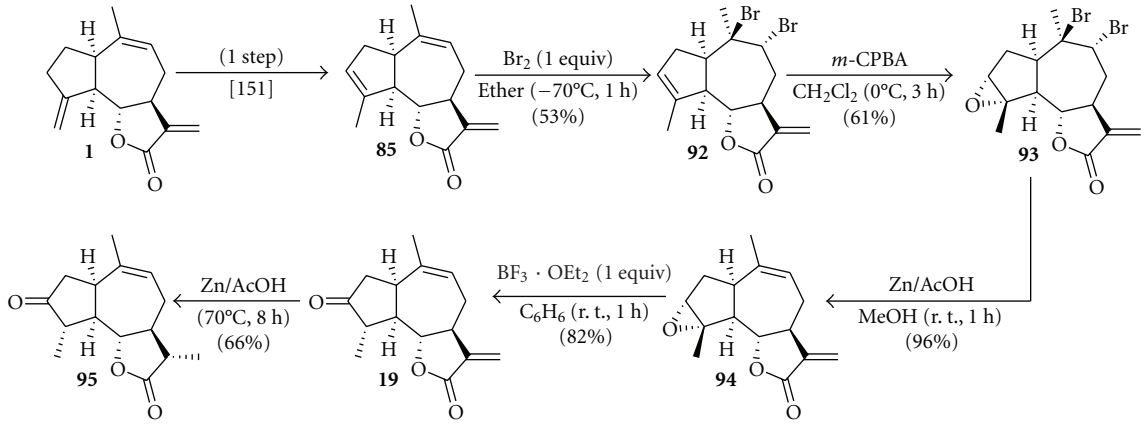
Scheme 20: Synthesis of dehydrocostus lactone (**10**).

was planned to be synthesized via the cationic intermediate **63**, that could be generated from the mesylate **64** through solvolytic rearrangement. The mesylate **64** could be obtained from α-santonin (**65**).

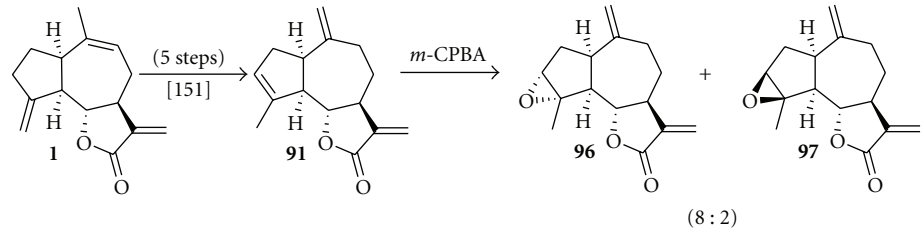
5.4. Stages of the Synthesis of Eremanthine. The steps that were employed by Yuuya et al. [12] to obtain eremanthine (**1**) starting from α-santonin (**65**), by the strategy outlined in Scheme 17, are depicted in Scheme 18. The starting material used for the synthesis of key intermediate **64** was the α,β-unsaturated ketone **66**, which was prepared from α-santonin (**65**) in six steps with an overall yield of 59% (Scheme 18). Ketalization of **66** and subsequent isomerization of double bond at C-2 by heating in ethylene glycol and TsOH gave the ketal **67** as the main product of that reaction. The acidic hydrolysis of compound **67** gave the ketone **68**, which was submitted to subsequent step of dehydrogenation with DDQ and TsOH to furnish the *exo*-dienone **69** as the major product. Treatment of this compound with zinc amalgam in refluxing AcOH gave γ,δ-unsaturated ketone **70**. Selective reduction of the C-1 carbonyl group of **70** with $LiAl(t\text{-}BuO)_3H$ furnished the desired β-alcohol **71** as the major product of that reaction. Mesylation of **71** with MsCl and pyridine gave the mesylate **64**. Solvolytic rearrangement of **64** with a solution of KOAc in AcOH provided a mixture of tetra-, tri-, and disubstituted olefins **72**, **21**, and **73** in a respective proportion of (2 : 1 : 2.4). After separation of crude product from the reaction by preparative HPLC, a fraction with a mixture (1 : 1.6 : 4) of **72**, **21**, and **73** was submitted to the following step of phenylselenylation with LDA and diphenyl diselenide to afford epimeric mixtures at C-11 of phenylseleno lactones **74** and **75** along with the lactone **76**. After separation by HPLC, the epimeric mixture of **75** at C-11 was submitted to oxidative elimination with H_2O_2 to furnish eremanthine (**1**) and the corresponding endo-unsaturated γ-lactone **77**.

6. Chemical Transformations of Eremanthine

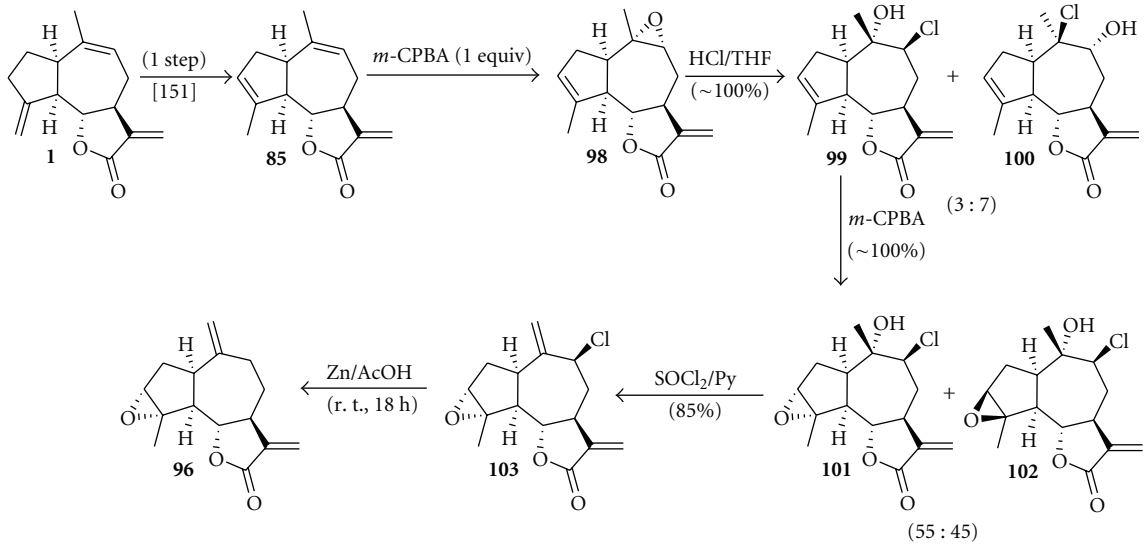
As eremanthine (**1**) was abundantly isolated from the oil of *Eremanthus elaeagnus* and *Vanillosmopsis erythropappa* [1, 2], there was initiated a program of chemical transformations of **1** aiming at the syntheses of other biologically active



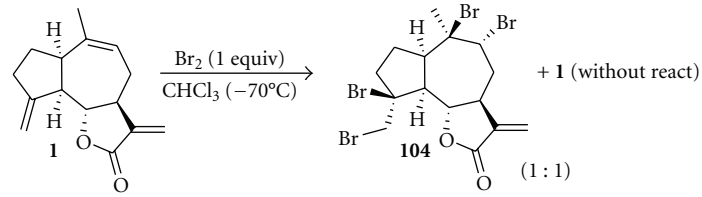
Scheme 21: Syntheses of eregoyazin (**19**) and eregoyazidin (**95**).



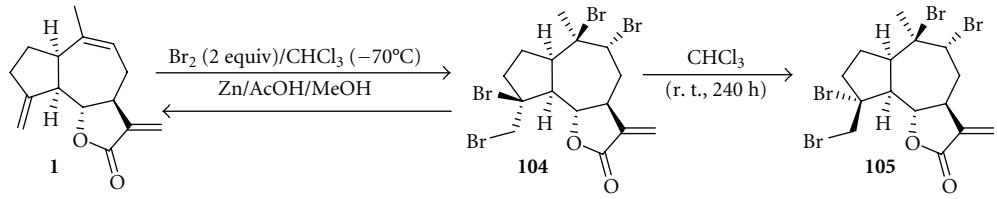
Scheme 22: Synthesis of (-)-estafiatin (**96**) in mixture with the isomer **97**.



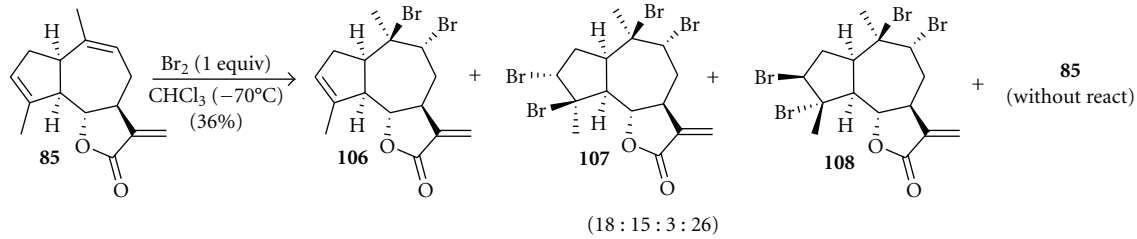
Scheme 23: Synthesis of (-)-estafiatin (**96**).



Scheme 24: Reaction of eremanthine (**1**) with equimolar amount of bromine.



Scheme 25: Reaction of eremanthine (**1**) with excess of bromine.



Scheme 26: Reaction of isoeremanthine (**85**) with bromine in chloroform.

derivatives as well as the preparation of less abundant naturally occurring lactones. As a result of this research program, several works of *M.S.* and *Ph.D.* degrees were accomplished using eremanthine (**1**) as object of study [15, 16, 144–150]. In the following subitems are described the syntheses of several eremanthine derivatives published in the period of 1972 to the current days.

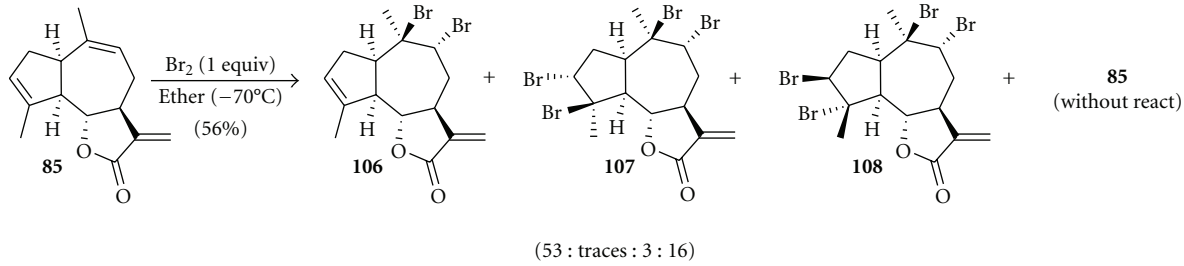
6.1. The First Chemical Transformations of Eremanthine. The first chemical transformations performed with eremanthine (**1**) were published in 1972 by Vichnewski and Gilbert [1] and are depicted in Scheme 19.

Dehydrogenation of eremanthine (**1**) with palladium by heating in nujol gave chamazulene (**78**), and the selective epoxidation of **1** yielded the epoxide **9**. Treatment of compound **9** with excess of BF_3-etherate furnished a product that was initially characterized as the ketone **79** [1]. Reinvestigation of this reaction by Garcia et al. [5] showed this structural assignment to be incorrect and the structure of the aldehyde **81**, resultant from a rearrangement, could be demonstrated by physical methods. Catalytic hydrogenation of eremanthine (**1**) resulted in the generation of a mixture of the isomers **80**. Reduction of **1** with $NaBH_4$ furnished a mixture of 3 products characterized as the compounds **82**, **83**, and **84**.

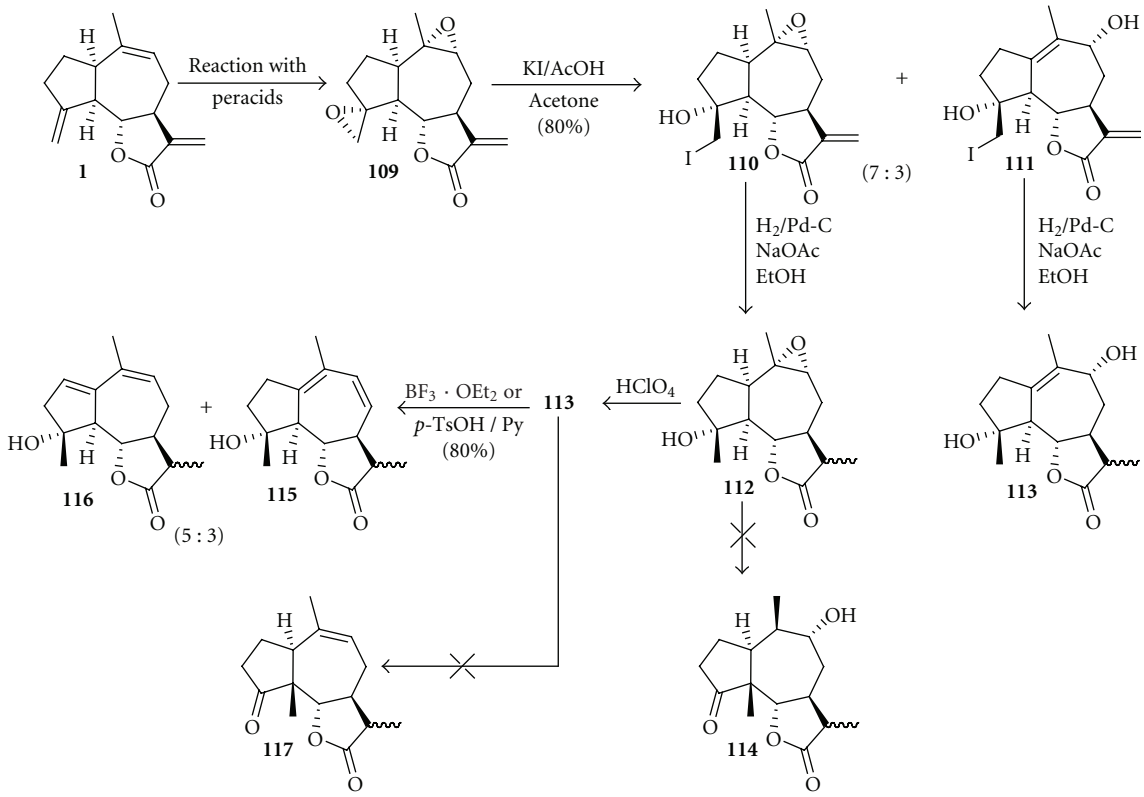
6.2. Chemical Transformations of Eremanthine for the Synthesis of Other Natural Guaianolides. In 1977 Maçaira et al. [151] published an article on the selective chemical modifications performed with eremanthine, aiming at the syntheses of other guaianolides of natural occurrence. As result of the chemical modifications performed with the substrate **1**, there were obtained the synthetic derivatives depicted in Scheme 20 besides the natural product dehydrocostus lactone (**10**), a guaianolide initially isolated from *Saussurea lappa* [152].

The isomerization of exocyclic double bond at five-membered ring of eremanthine (**1**) was achieved treating this compound with excess of $BF_3 \cdot OEt_2$. In these conditions isoeremanthine (**85**) could be obtained in yields ranging from 65 to 80%, according to scale of the substrate, quantity of $BF_3 \cdot OEt_2$, and reaction time. To ensure that the isomerization of **1** to **85** did not result in change of the configuration at C-1 and C-5, isoeremanthine (**85**) was treated with NBS in a mixture of dioxane-H_2O. The formation of the dibromoether **86** did confirm the *cis* fusion at the five- and seven-membered rings of isoeremanthine. The aldehyde **87** could be obtained selectively, without isomerization of exocyclic double bond at five-membered ring, by treating epoxide **9** with equimolar amount of $BF_3 \cdot OEt_2$. When epoxide **9** was treated with concentrated HCl in THF, the chlorohydrins **88** and **89** were isolated in a respective proportion of (6 : 5). Treatment of compound **88** with a mixture of thionyl chloride and pyridine, at low temperature, gave allylic chloride **90**. Dechlorination of **90** in acid medium with zinc and MeOH furnished a compound identified as dehydrocostus lactone (**10**). The isomerization of exocyclic double bond at five-membered ring of **10** was achieved through the reaction of this compound with $BF_3 \cdot OEt_2$, at the same conditions used to convert eremanthine (**1**) into isoeremanthine (**85**). In those conditions isodehydrocostus lactone (**91**) was obtained.

6.3. Syntheses of Eregoyazin and Eregoyazidin. In order to confirm the structures of eregoyazin (**19**) and eregoyazidin (**95**), two guaianolides isolated from *Eremanthus goyazensis* by Vichnewski et al. [153], the syntheses of these compounds were accomplished according to the sequence of reactions depicted in Scheme 21 [153, 154]. The reaction of isoeremanthine (**85**) with one equivalent of bromine at −70°C gave a mixture from which the compound **92** could be isolated. Peracid oxidation of **92** from the less hindered face



Scheme 27: Reaction of isoeremanthine (**85**) with bromine in ether.

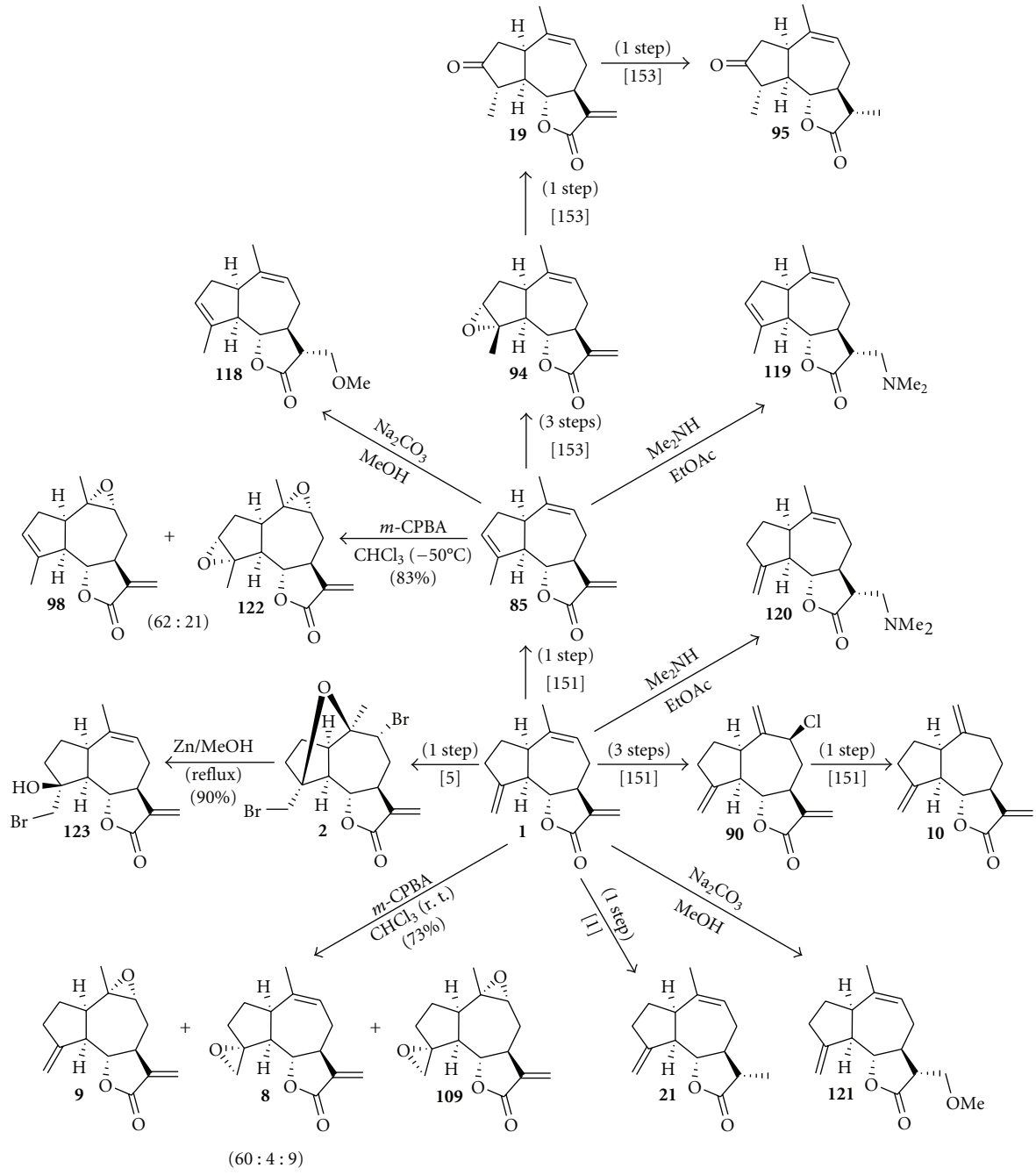


Scheme 28: Biomimetic transformations of eremanthine (**1**).

afforded mainly the α-epoxide **93**. Exposure of this epoxide to methanolic zinc resulted in debromination to furnish compound **94**. Treatment of **94** with $BF_3 \cdot OEt_2$afforded a substance identical in all aspects with eregoyazin (**19**). Further reduction of **19** with zinc in hot glacial acetic acid yielded eregoyazidin (**95**).

6.4. Synthesis of (-)-Estafiatin. The stereoselective synthesis of the natural product (-)-estafiatin (**96**), a sesquiterpene lactone isolated from *Artemisia mexicana* [155], was developed by Rabi et al. [154, 156]. The sequences of reactions used for the synthesis of this natural product are depicted in Schemes 22-23. Initially the triene **91**, obtained from eremanthine (**1**) for the sequence of reactions outlined in Scheme 20, was submitted to epoxidation with *m*-chloroperbenzoic acid to furnish a mixture characterized as the epoxides **96** and **97** (8 : 2,^{1}H NMR). The major isomer showed identical properties with the naturally occurring (-)-estafiatin (**96**) (Scheme 22) [156].

The compound (-)-estafiatin (**96**) was also obtained by the sequence of reactions depicted in Scheme 23 [154, 156]. The reaction of isoeremanthine (**85**) with equimolar amount of *m*-chloroperbenzoic acid resulted in almost exclusive formation of epoxide **98** which upon reaction with HCl in THF gave a mixture of chlorohydrins **99** and **100** (3 : 7). Epoxidation of **99** led to a nearly equimolar

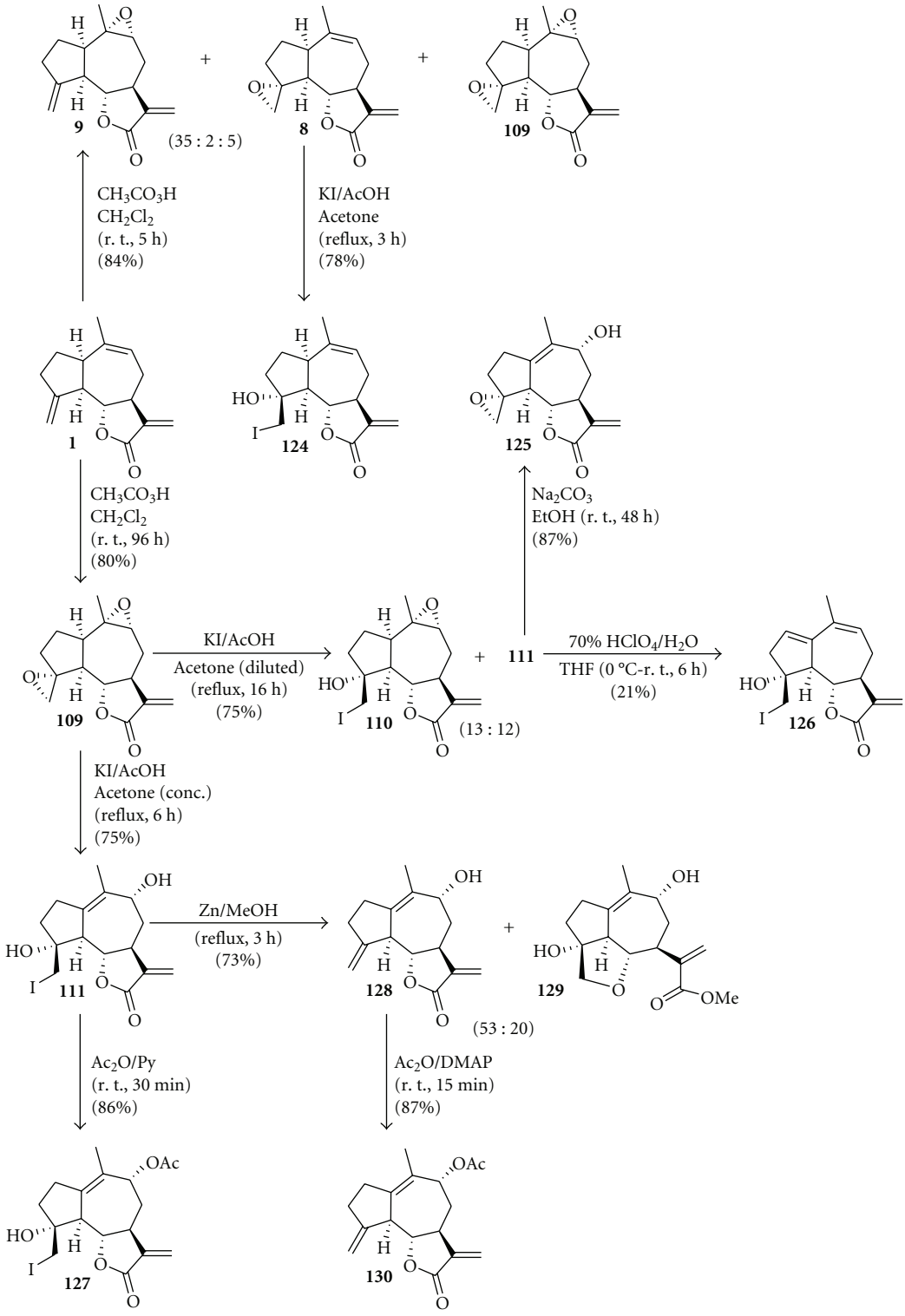


Scheme 29: Syntheses of eremanthine derivatives to the study of ^{13}C NMR spectroscopy.

mixture of epoxides **101** and **102** (55 : 45). Dehydration of **101** with a mixture of $SOCl_2$ and pyridine furnished **103**. Dechlorination of this compound with zinc yielded a substance identified as (-)-estafiatin (**96**).

6.5. Reaction of Eremanthine and Isoeremanthine with Bromine. The search for a selective method to protect the most nucleophilic 9,10-double bond of eremanthine (**1**) led to the investigation of eletrophilic addition of bromine to this compound and also to isoeremanthine (**85**). The conditions that were employed by Garcia et al. [157] to study this addition reaction are described in Schemes 24–27. When eremanthine (**1**) was allowed to react with one equivalent of bromine at kinetic conditions, an equimolar mixture of tetrabromide **104** and **1** could be detected by ^1H NMR spectroscopy (Scheme 24).

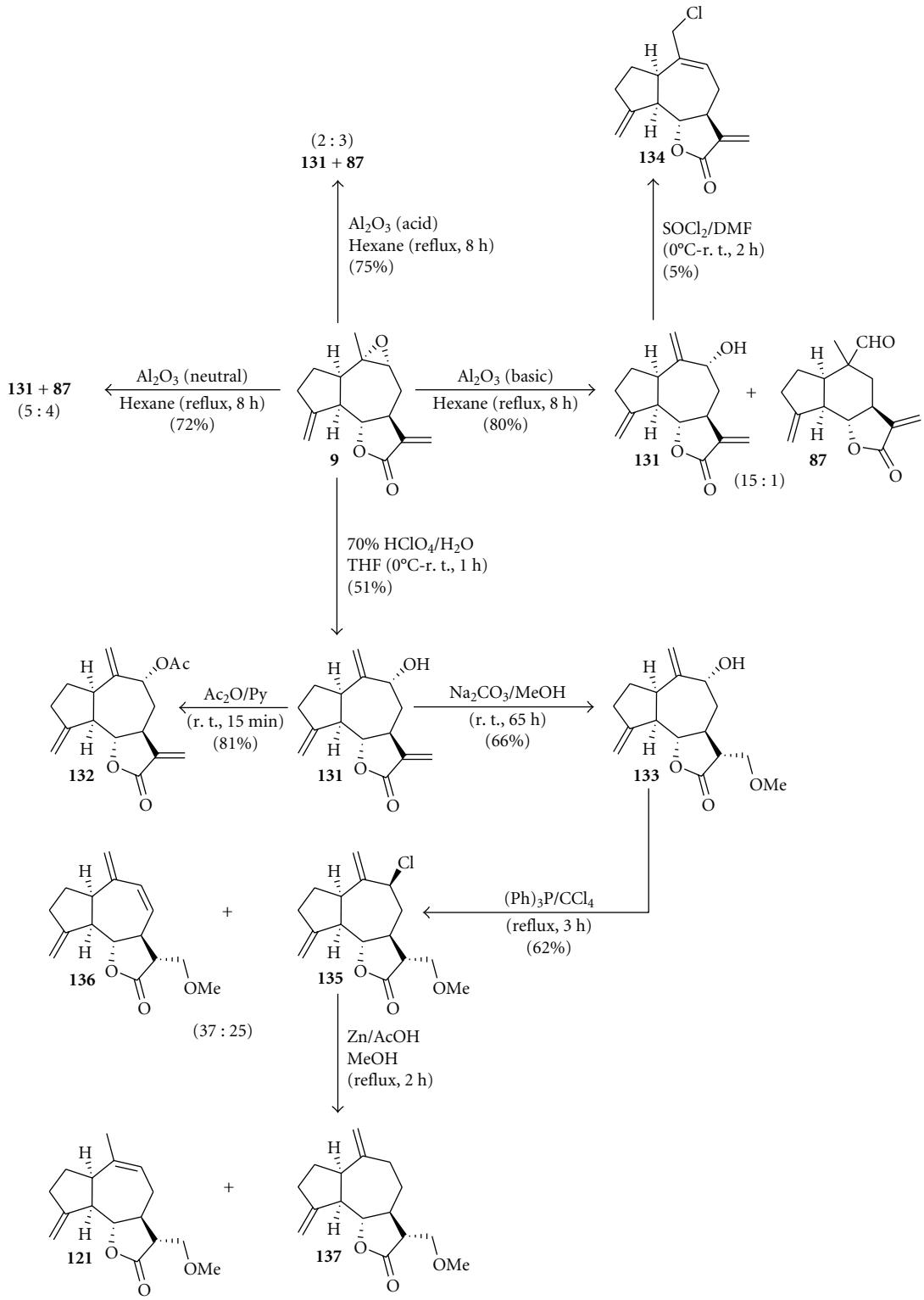
Addition of two equivalents of bromine to eremanthine (**1**) resulted in the exclusive formation of tetrabromide **104**. Reaction of this compound with zinc in methanol regenerated eremanthine (**1**) in quantitative yield. When



Scheme 30: Study on the chemical reactivity of epoxides derived from eremanthine (**1**).

a solution of compound **104** in $CHCl_3$ was left at room temperature during 240 hours, the tetrabromide **105** was obtained (Scheme 25). The inversion of configuration at C-4 in this reaction was attributed to stereoelectronic repulsion between the β-oriented bromine atoms at C-4 and C-10 at the substrate **104**.

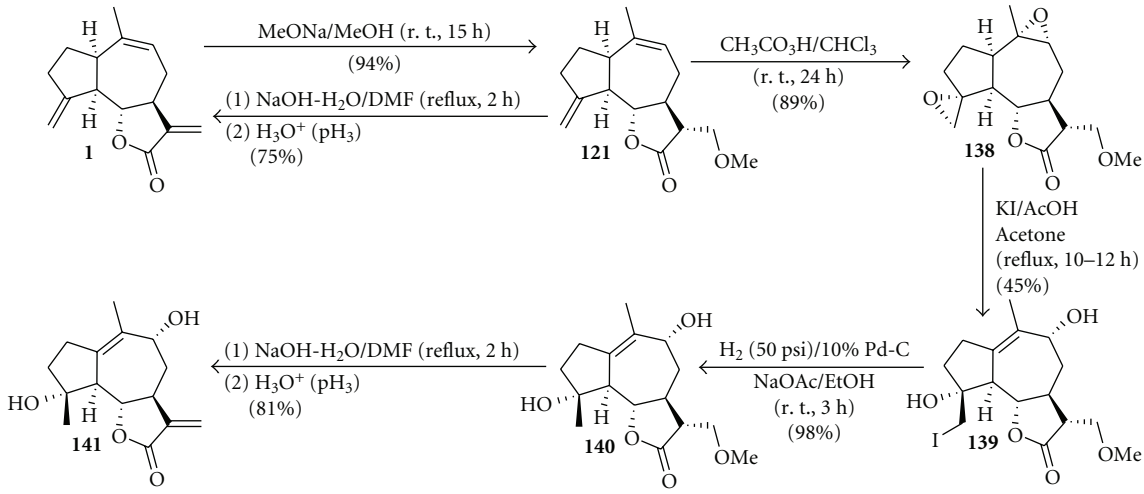
A complex mixture of products was obtained when isoeremanthine (**85**) was submitted to reaction with one



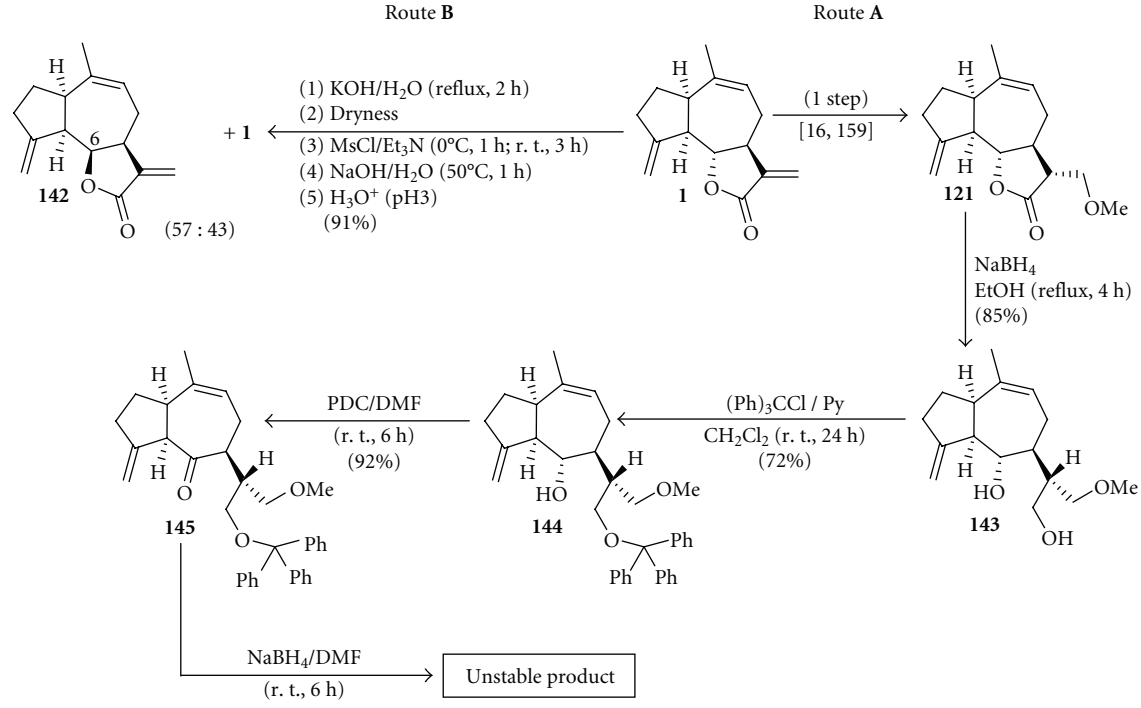
Scheme 31: Reaction conditions studied to the opening of epoxide **9**.

equivalent of bromine at kinetic conditions (Schemes 26-27). A detailed discussion on the probable mechanisms for these reactions of bromine addition is presented in the article published in 1980 [157].

6.6. Biomimetic Transformations of Eremanthine. Chemical transformations of eremanthine (**1**) were studied by Rodrigues [148] aiming to obtain subsidies for the biogenetic hypothesis of pseudoguaianolides formation. The sequence

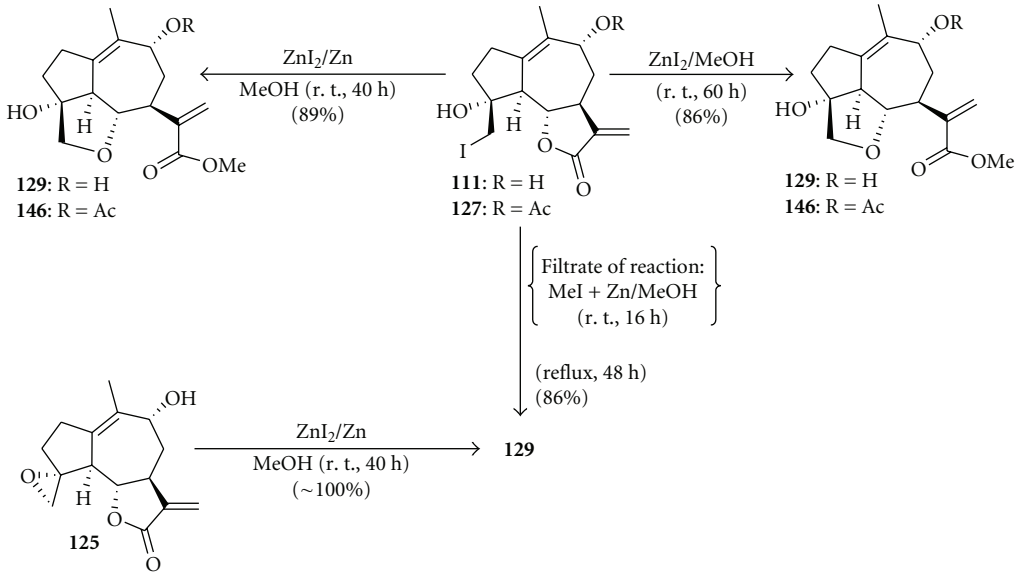


Scheme 32: Synthesis of the diol **141**.

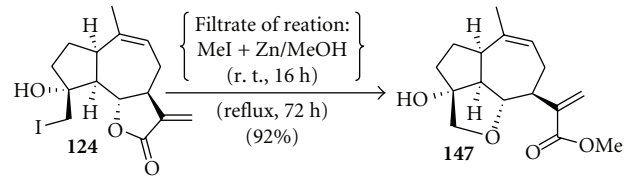


Scheme 33: Synthesis of 6-*epi*-eremanthine (**142**).

of reactions developed in that study is depicted in Scheme 28. Epoxidation of eremanthine (**1**) gave the diepoxide **109** which was submitted to reaction with KI and acetic acid to furnish a mixture of epoxide **110** and allylic alcohol **111**. Catalytic hydrogenation of these compounds gave, respectively, the epoxide **112** and diol **113**. Treatment of compound **112** with $HClO_4$ resulted in the formation of diol **113** instead of the pseudoguaianolide **114**. Reaction of diol **113** with the acids $BF_3 \cdot OEt_2$ or *p*-TsOH furnished a mixture of dienes **115** and **116** instead of the desired compound **117** with pseudoguaianolide skeleton. The nonformation of the substances **114** and **117** with pseudoguaianolide skeleton reinforces, once again, the hypothesis that the formation of those compounds with lactonic fusion at the C-6 and C-7 positions need a β-oxygenated function at the C-6 position of the precursor guaianolide for the occurrence of



Scheme 34: Methanolysis of the iodohydrins **111** and **127** and epoxide **125**.

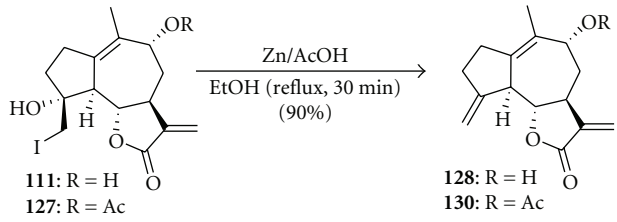


Scheme 35: Methanolysis of the iodohydrin **124**.

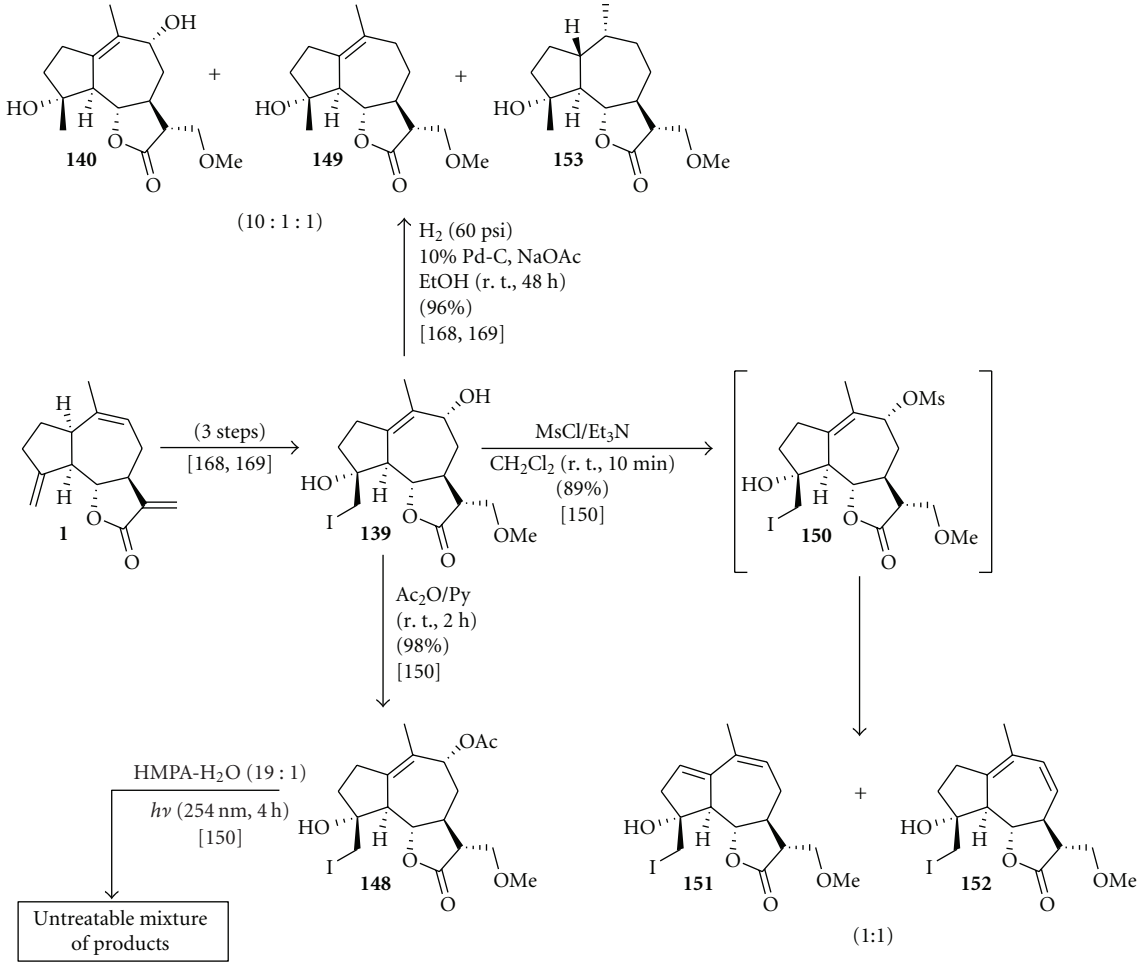
the rearrangements preconized by the biogenesis hypothesis of the ambrosanolides (Scheme 13).

6.7. Study of ^{13}C NMR Spectroscopy on Eremanthine Derivatives. In 1981 da Silva et al. [158] published an article with the chemical shifts assigned to the carbons of naturally occurring guaianolides eremanthine (**1**), dehydrocostus lactone (**10**), eregoyazin (**19**), eregoyazidin (**95**), and other semisynthetic lactones derived from eremanthine (**1**). A detailed discussion correlating the data of ^{13}C NMR with the probable conformations at the seven-membered ring of the investigated guaianolides is presented in the article. The sequences of reactions employed to synthesize the eremanthine derivatives used in the experiments of ^{13}C NMR spectroscopy of that article are depicted in Scheme 29. The lactones **2**, **9**, **10**, **19**, **21**, **85**, **90**, **94**, and **95** were obtained by the sequences of reactions outlined in Schemes 1 and 19–21. The others were prepared from known substances by standard simple procedures. The compounds **118**, **119**, **120**, and **121** were prepared by reaction of eremanthine (**1**) or isoeremanthine (**85**) with $MeOH/Na_2CO_3$ or $Me_2NH/EtOAc$. The reaction of eremanthine (**1**) with *m*-chloroperbenzoic acid in $CHCl_3$ at room temperature yielded a mixture of epoxides **9**, **8**, and **109**. The compounds **98** and **122** were obtained by reaction of isoeremanthine (**85**) with *m*-chloroperbenzoic acid in $CHCl_3$ at low temperature in a respective proportion of (62 : 21). The bromohydrin **123** was prepared by reaction of dibromoether **2** with zinc in refluxing MeOH.

6.8. Studies on the Chemical Reactivity of Epoxides Derived from Eremanthine. The syntheses of guaianolides precursors of the series $\Delta^{1,10}$ and $\Delta^{10,14}$ starting from epoxides derived from eremanthine (**1**) were studied by Ferreira [15] (Schemes 30-31). The epoxidation of eremanthine (**1**) with peracetic acid during 5 hours gave a mixture of epoxides **9**, **8**, and **109** in a respective proportion of (35 : 2 : 5) (Scheme 30). When this same reaction was performed during 96 h, the diepoxide **109** was obtained as a single product. Treatment of a diluted solution of diepoxide **109** in acetone with KI and AcOH furnished a mixture of iodohydrin epoxide **110** and iodohydrin allylic alcohol **111** in a respective proportion of (13 : 12). When diepoxide **109** was submitted to this same reaction in a concentrated solution of acetone, the iodohydrin **111** could be isolated as a single product. The iodohydrin **124** was obtained by treatment of monoepoxide **8** with KI and AcOH in acetone. The transformation of iodohydrin **111** into epoxide **125** was achieved by an intramolecular reaction of nucleophilic substitution by using a solution of Na_2CO_3 in

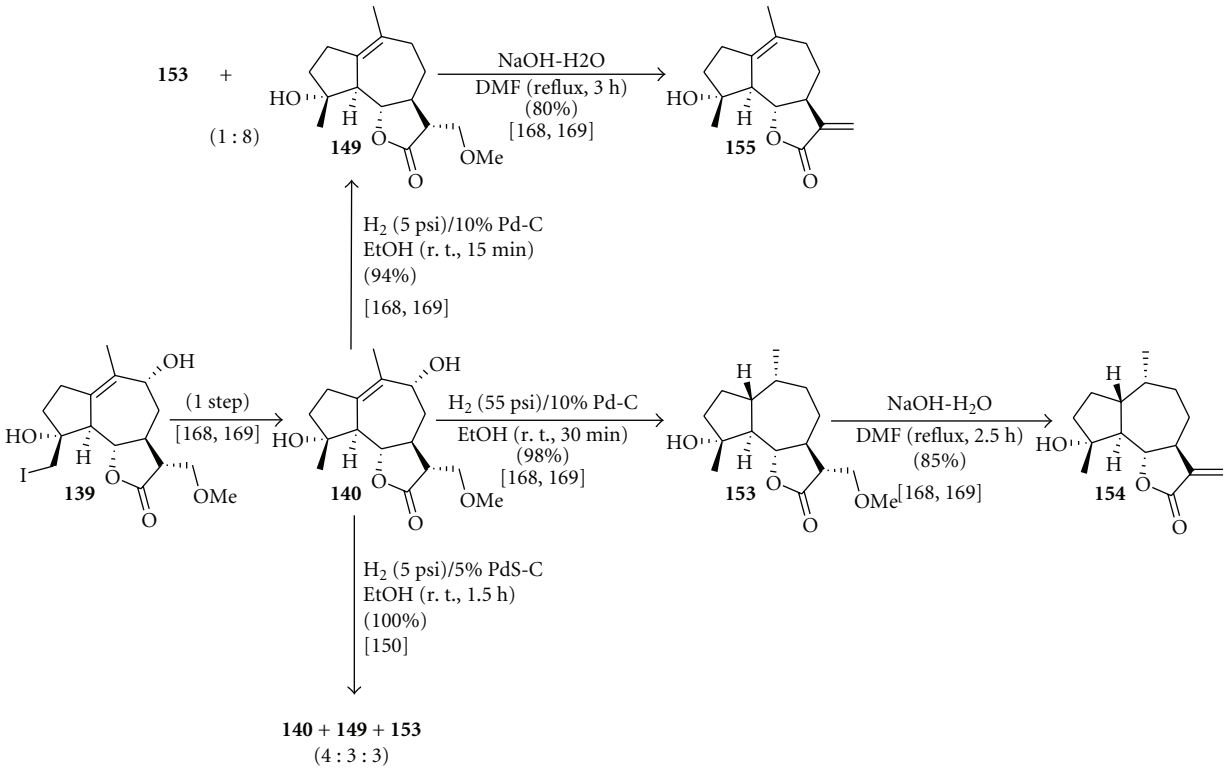


Scheme 36: Synthesis of the trienes **128** and **130**.



Scheme 37: Initial attempts to the synthesis of compound **149**.

ethanol. Treatment of **111** in THF with an aqueous solution of $HClO_4$ yielded the diene **126** and the acetylation of **111** with Ac_2O and pyridine gave allylic acetate **127**. When the iodohydrin **111** was submitted to elimination reaction with zinc in refluxing MeOH, the desired triene **128** was obtained along with another product identified as the oxacycloguaiane methyl ester **129**. Acetylation of allylic alcohol **128** with acetic anhydride and DMAP yielded the allylic acetate **130**. The opening of epoxide **9** was studied using different conditions (Scheme 31). The reaction of **9** in THF with an aqueous solution of $HClO_4$ yielded allylic alcohol **131** and the opening of epoxide **9** with aluminum oxide (neutral, acid or basic) in refluxing hexane furnished the desired product **131** accompanied by another compound identified as the aldehyde **87**. Acetylation of allylic alcohol **131** with Ac_2O and pyridine gave the acetate **132**. The protection of α-methylene-γ-lactone of **131** was achieved by reaction of this compound with methanol and Na_2CO_3 to afford the adduct **133**. Attempts to deoxygenate the C-9 position of compounds **131** and **133** were performed with limited success. The reaction of allylic alcohol **131** with thionyl chloride and DMF furnished a product identified by attempt



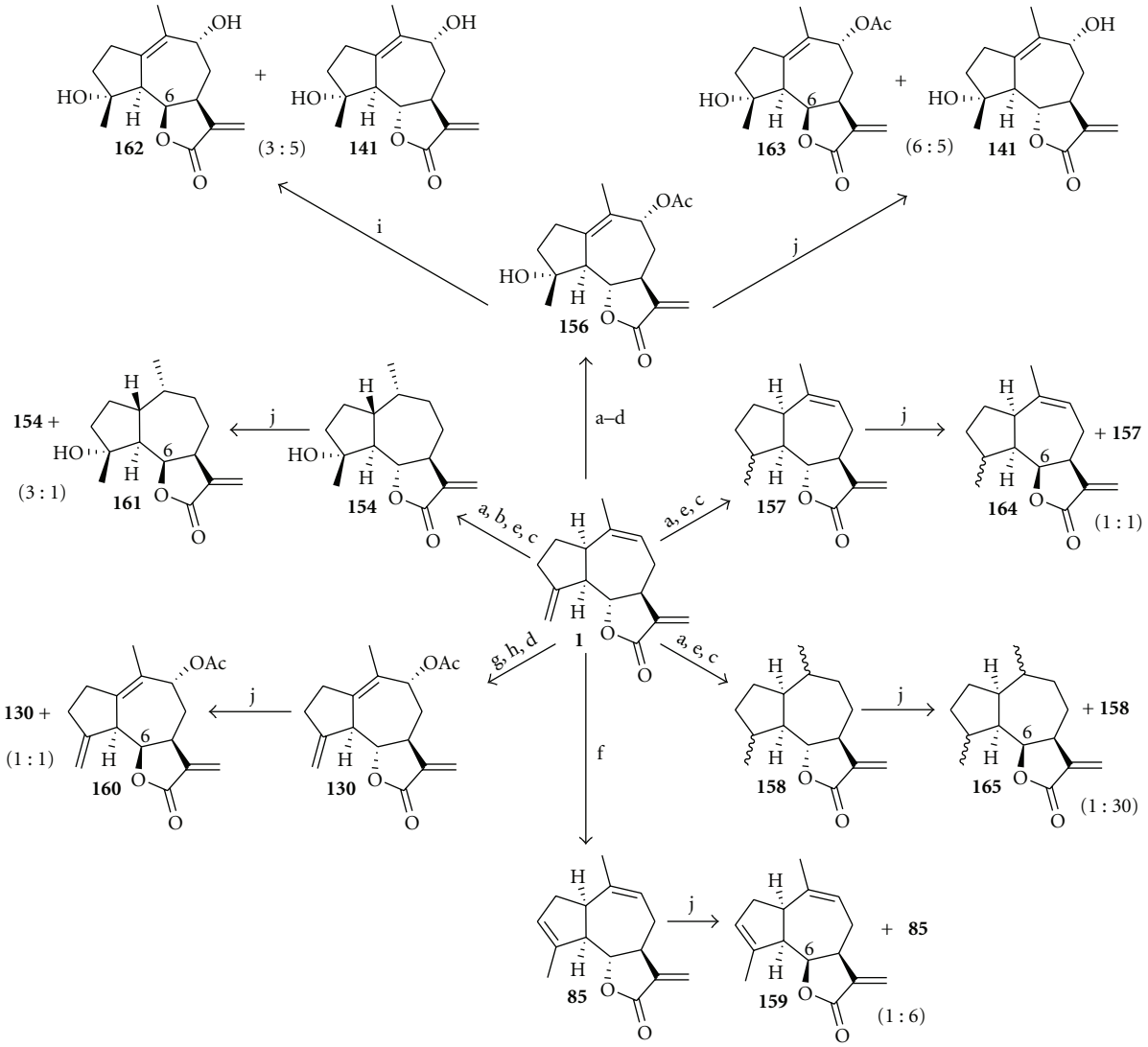
Scheme 38: Syntheses of micheliolide (**155**) and 1*R*, 10*R*-dihydromicheliolide (**154**).

as allylic chloride **134**. On the other hand, the reaction of **133** with triphenylphosphine and CCl_4 gave a mixture of desired product **135** accompanied by another compound identified as the conjugate diene **136**. Dechlorination of **135** with zinc and AcOH in refluxing MeOH furnished a mixture of two products with the same R_f of authentic samples of the methanol adducts of eremanthine (**121**) and dehydrocostus lactone (**137**).

6.9. Study on the Chemical Reactivity of Eremanthine: The α-Methylene-γ-Lactone Moiety. With the objective of extending the study on the chemical transformations of eremanthine (**1**) to the lactonic ring, Fantini [16] developed her *Ph.D.* thesis focusing the α-methylene-γ-lactone of that substance and of its synthetic derivatives. The syntheses of compounds used in that study are outlined in Schemes 32–35.

The search for a protective group of α-methylene-γ-lactones resistant in certain reaction conditions, for example, catalytic hydrogenation, led to the synthesis of methanol adduct of eremanthine (**121**). It was verified that in basic conditions (aqueous NaOH, DMF, reflux), the α-methylene-γ-lactone could be regenerated in high yields [159]. The use of methoxyl as protective group for the α-methylene-γ-lactone of eremanthine (**1**) was accomplished with success during the synthesis of diol **141** (Scheme 32) [16]. The reaction of eremanthine (**1**) with a solution of MeONa in methanol gave the adduct **121**. Treatment of this compound with a solution of peracetic acid in chloroform yielded diepoxide **138**. The cleavage of oxiranic rings of **138** with KI and acetic acid in refluxing acetone furnished iodohydrin **139**. Catalytic hydrogenation of **139** with hydrogen, Pd-C, and sodium acetate in EtOH yielded diol **140**. This substance was submitted to subsequent step of treatment with an aqueous solution of NaOH in refluxing DMF to give, after aqueous acid work up, the α-methylene-γ-lactone **141** as the main product of this reaction.

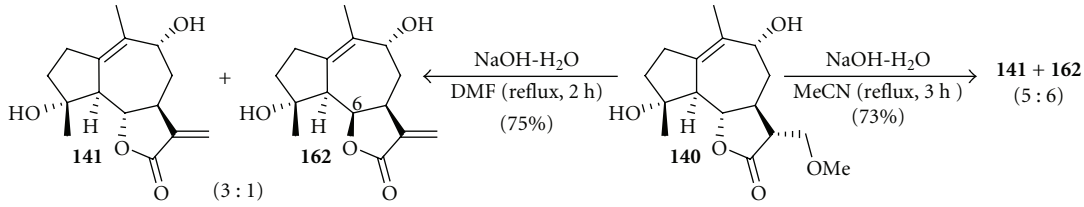
The inversion of configuration at C-6 position of eremanthine (**1**), aiming at the synthesis of 6-*epi*-eremanthine (**142**), was studied by the two sequences of reactions depicted in Scheme 33 [16, 160]. In the route **A**, the inversion of configuration at C-6 position of **1** was planned by the method of oxidation-reduction of secondary hydroxy group in this position. The reduction of carboxy group of the lactonic ring at methanol adduct **121** with $NaBH_4$ in ethanol gave diol **143**. In the next step, this compound was submitted to protection of primary hydroxyl with $(Ph)_3CCl$ and pyridine in CH_2Cl_2 to furnish compound **144**. The oxidation of secondary hydroxyl at **144** was performed with pyridinium dichromate in DMF to afford the ketone **145**. Treatment of **145** with sodium borohydride in DMF furnished an unstable product of difficult purification. With this unsatisfactory result, the synthesis of **142** was studied by the route **B**. The inversion of configuration at C-6 of eremanthine (**1**) was achieved by displacement of intermediate mesylate generated in this position to afford a mixture of **1** and the unstable 6-*epi*-eremanthine (**142**) (43 : 57, ^{1}H NMR). The instability of **142** was attributed to steric effects at the hydroazule system.



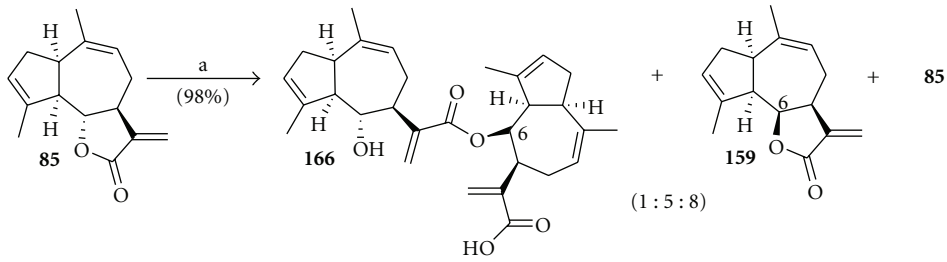
Scheme 39: Syntheses of the substrates **85**, **130**, **154**, and **156–158** and their epimers at C-6 positions (**159–165**). (a) MeONa, MeOH; (b) (i) AcO_2H, CH_2Cl_2; (ii) KI, AcOH, acetone; (iii) H_2, Pd-C, NaOAc, EtOH; (c) NaOH-H_2O, DMF; (d) Ac_2O, pyridine; (e) H_2, Pd-C, EtOH; (f) $BF_3.OEt_2$, benzene; (g) (i) AcO_2H, $CHCl_3$; (ii) KI, AcOH, acetone; (h) Zn, AcOH, EtOH; (i) (i) KOH-H_2O (ii) Dryness; (iii) MsCl, Et_3N, DMSO; (iv) NaOH-H_2O; (v) HCl-H_2O; (j) (i) KOH-H_2O (ii) Dryness; (iii) MsCl, Et_3N, THF; (iv) NaOH-H_2O; (v) HCl-H_2O.

After the synthesis of triene **128**, obtained in mixture with oxacycloguaiane methyl ester **129** (Scheme 30), there was initiated a study aiming at to optimize the formation of compound **129** [15, 16, 161, 162]. As a result of this study, the furanic derivatives **129**, **146**, and **147** were obtained (Schemes 34-35). There is a discussion evaluating the structures of reactive eremanthine derivatives (**111**, **124**, **125**, and **127**) in comparison with other inert compounds obtained from eremanthine (**1**) as well as the reactive species responsible for the methanolysis of the lactonic ring in that reaction as reported in an article published in 1986 by Fantini et al. [163].

The reaction of iodohydrin **111** with zinc in refluxing methanol (Scheme 30) showed that furanic derivative **129** was formed after the triene **128**. It was also verified that triene **128** did not generate the compound **129**. Starting from these observations, it was presumed that the reactive species responsible for the formation of compound **129** was a by-product from the reaction of iodohydrin **111** with zinc (IZnOH) [16]. As an attempt to simulate the reactional system of iodohydrin **111** with zinc in methanol, there was developed a reagent that in fact converted directly the substrate **111** into oxacycloguaiane **129**. This reagent was the filtrate of a mixture containing MeI, zinc, and methanol left in contact for 16 h at room temperature [15]. When iodohydrin **111** was submitted to reaction with this reagent under reflux during 48 h, the oxacycloguaiane **129** was obtained as a single product (Scheme 34). When iodohydrin **124** was submitted to similar conditions, the compound **147** was obtained after 72 h of reaction (Scheme 35) [15]. In the following stage this reaction was performed with ZnI_2. When



Scheme 40: Inversion of configuration at C-6 position of the diol **141** occurred at the step of methanol elimination on adduct **140**.



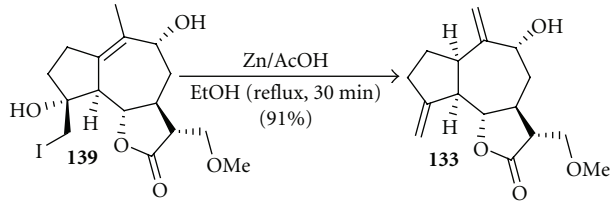
Scheme 41: Synthesis of the compound **166** in mixture with the lactone **159**: (a) (i) KOH-H_2O; (ii) Dryness; (iii) MsCl, Et_3N, THF (conc.); (iv) NaOH-H_2O; (v) HCl-H_2O.

iodohydrins **111**, and **127** were allowed to react with ZnI_2 in methanol at room temperature, the respective furanic derivatives **129** and **146** were obtained (Scheme 34). It was also verified that the addition of zinc to reactional mixture accelerated the formation of these compounds. When the iodohydrins **111**, **127** and epoxide **125** were allowed to react with a mixture of ZnI_2, zinc, and methanol at room temperature for 40 h, there was verified the total conversion of these substrates to respective products **129** and **146** (Scheme 34).

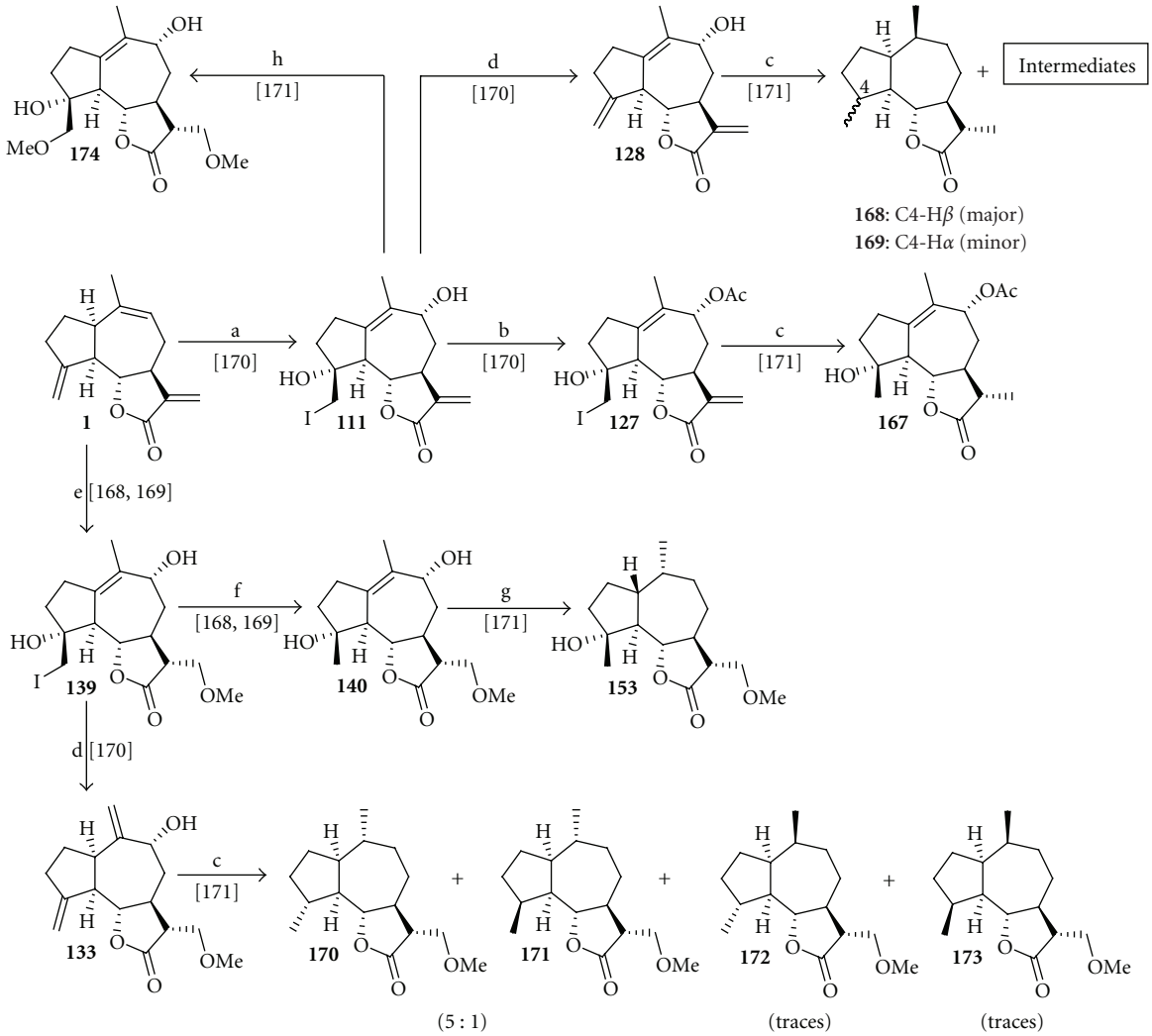
*6.10. Synthesis of the Trienes **128** and **130**.* Besides the reactions of her *Ph.D. thesis* [16], described in the previous subitem (6.9), Fantini developed the synthesis of the trienes **128** and **130** starting from the respective iodohydrins **111** and **127** as a Researcher Professor of the Department of Chemistry at the Rural Federal University of Rio de Janeiro (UFRRJ). The optimized conditions of those reactions were reported in a congress abstract [164] and are depicted in Scheme 36.

6.11. Study of the Inversion Reaction of the Lactonic Fusion on Eremanthine Derivatives and Synthesis of Micheliolide. The last studies with eremanthine (**1**) were performed by Alves [150]. These studies were developed aiming at the syntheses of substrates derived from the lactone **1** with different structural features to be used in the next stage of inversion of the lactonic fusion employing the conditions depicted in Scheme 33 (route B), aiming to get epimers more stable than 6-*epi*-eremanthine (**142**) previously synthesized [16, 160]. That study of inversion of the lactonic fusion was also planned to obtain a substance with the necessary structural requirements for an eventual investigation of the biomimetic transformation of guaianolide into pseudoguaianolide, discussed in the text of this review at the subitems 3.1 (Scheme 13) and 6.6 (Scheme 28). There was also studied the synthesis of micheliolide, a naturally occurring substance initially isolated from *Michelia compressa* with relevant biological activity [165]. In the following subitems are described the sequences of reactions that were developed aiming to attain these objectives [150, 166–170] as well as the results of the study from the reactions of catalytic hydrogenation and methanol addition to α-methylene-γ-lactone of eremanthine derivatives [171].

6.11.1. Study on the Synthesis of Micheliolide. The synthesis of micheliolide (**155**) was studied by the sequences of reactions depicted in Schemes 37 and 38. Initial attempts to deoxygenate the C-9 position of acetate **148** and iodohydrin **139** with concomitant hydrogenolysis of the bond C15-I in these compounds were unsuccessful [150]. When the allylic acetate **148** was submitted to photolysis conditions in a solution of HMPA and water, using the procedure reported by Deshayes et al. [172], an untreatable mixture of products was obtained instead of the desired compound **149** (Scheme 37). On the other hand, treatment of iodohydrin **139** with MsCl and Et_3N in dichloromethane, by the procedure of Crossland and Servis [173], generated a mixture of conjugate dienes **151** and **152** instead of the intermediate mesylate at C-9 position (**150**), which would be used in the next step of hydrogenolysis with $NaBH_3CN$ in HMPA by the procedure of Hutchins et al. [174], aiming to obtain the target molecule **149**. The author is disregarding in this review the preliminary results reported before about this reaction [166]. On that occasion this reaction was described in the following way: treatment of **139** with $MsCl/Et_3N/CH_2Cl_2$ (r. t.) followed by

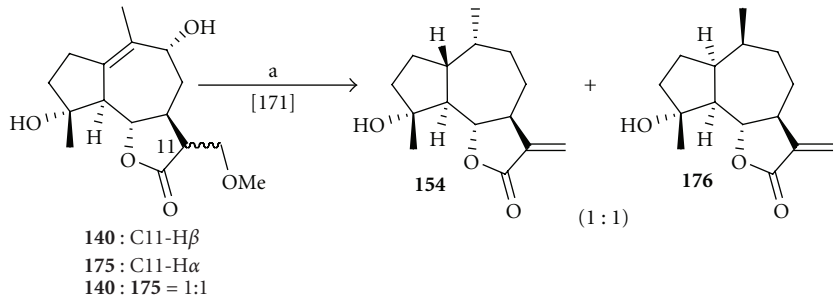


Scheme 42: Synthesis of the allylic alcohol **133**.



Scheme 43: Preparation of the substrates **111**, **127**, **128**, **133**, and **140** and subsequent reactions of catalytic hydrogenation as well as methanol addition to α-methylene-γ-lactone of the iodohydrin **111**. (a) (i) AcO_2H, $CHCl_3$; (ii) KI, AcOH, acetone; (b) Ac_2O, pyridine; (c) H_2, Pd-C, EtOH; (d) Zn, AcOH, EtOH; (e) (i) MeONa, MeOH; (ii) AcO_2H, CH_2Cl_2; (iii) KI, AcOH, acetone; (f) H_2, Pd-C, NaOAc, EtOH; (g) H_2, Pt-C, EtOH; (h) MeONa, MeOH.

$NaBH_3CN$/HMPA (r. t.) furnished dienes ($\Delta^{1,2}$, $\Delta^{9,10}$) (^{1}H NMR 200 MHz, $CDCl_3$, 5.85, m, 1H, C2-H) [166]. On that time, in which that abstract was written with the results from scientific initiation of the author, his supervisor described the ^{1}H NMR data of only one elimination product (compound **151**). For the occasion of the *M.S.*, the author obtained the ^{1}H NMR spectrum of the crude product from the mesylation reaction described in Scheme 37 and he detected the presence of the conjugate dienes **151** and **152** (1 : 1) [150], concluding that the mesylate **150** is formed and it



Scheme 44: Synthesis of the compound **176** in mixture with the lactone **154**: (a) (i) H_2, Pd-C, EtOH; (ii) NaOH-H_2O, DMF.

is instantly converted to the final products of elimination (**151** and **152**). Therefore, the subsequent and unnecessary step of reduction with $NaBH_3CN$ was not performed on that occasion of his academic formation (*M.S.*). It is important to emphasize in this point that the strategy aiming to deoxygenate the C-9 position of allylic acetate **148** and allylic mesylate **150** was unsuccessful due to the following reasons. In the case of the photolysis reaction, the method described by Deshayes et al. [172] is applied to nonactivated carboxylic esters. Evidently the allylic acetate at the substrate **148** is an activated moiety but the chemistry is an experimental science and the author, in that time, should test this reaction with the substance **148** to confirm experimentally the data of literature and know how to execute the reaction in a photochemical reactor. In the case of the attempt to isolate the allylic mesylate **150**, this was impossible because electron-withdrawing groups such as OSO_2R increase the acidity of the hydrogen that is lost in any elimination mechanism (E1, E2, and E1cB) when those groups are conjugated with double bond [175, page 893]. Once again in that time of scientific initiation in which this reaction was performed for the first time, the author had little knowledge of advanced organic chemistry and he should make that reaction to confirm the data described in literature on conjugate eliminations [175, page 900], in which allylic mesylate undergoes elimination reaction to furnish conjugate dienes. That result was also important to confirm the elimination reactions previously occurred with the allylic derivatives of eremanthine **113** (Scheme 28) and **111** (Scheme 30) yielding the respective conjugate dienes **115**-**116** [148] and **126** [15]. With those unsatisfactory results, the synthesis of compound **149** was attempted by catalytic hydrogenation of iodohydrin **139** with NaOAc in EtOH, using a longer reaction time and a higher hydrogen pressure than those commonly used to get diol **140** (Scheme 32). In those reaction conditions (60 psi of hydrogen, r. t., 48 h), the desired compound **149** was obtained as the minor product in mixture with diol **140** and compound **153** (Scheme 37) [168, 169].

In the next stage, the hydrogenolysis reaction aiming at the synthesis of compound **149** was performed with the substrate **140** (Scheme 38), using the hydrogenolysis conditions of allylic alcohols reported by House [176, page 23]. When diol **140** in EtOH was submitted to hydrogenation (55 psi of hydrogen) with Pd-C, a compound identified as **153** was obtained as a result of hydrogenolysis of the bond C9-OH and hydrogenation of tetrasubstituted double bond C1-C10. Attempt to perform only hydrogenolysis of the bond C9-OH on diol **140** without reduction of double bond C1-C10 was carried out using a less reactive catalyst (PdS-C) than Pd-C in EtOH under low hydrogen pressure (5 psi). After the reaction time (1.5 h, r. t.), the substrate **140** was recovered in mixture with **149** and **153** in a respective proportion of (4 : 3 : 3) [150]. Hydrogenation of allylic alcohol **140** using a low hydrogen pressure (5 psi) during a short reaction time (15 min) generated the target compound **149** as the main product of this reaction in mixture with the lactone **153** in a respective proportion of (8 : 1), according to ^{1}H NMR spectrum of crude product from that reaction. The probable causes from the low reactivity of allylic alcohol **139** in catalytic hydrogenation reaction with NaOAc, in opposition to the high reactivity of the similar allylic alcohol **140** without the use of NaOAc, were reported in a recently published work [171]. Elimination of methanol on the compounds **149** and **153** generated the respective α-methylene-γ-lactones micheliolide (**155**) and 1*R*,10*R*-dihydromicheliolide (**154**) (Scheme 38).

6.11.2. Study of the Inversion Reaction of the Lactonic Fusion on Eremanthine Derivatives. The inversion of configuration at C-6 position on eremanthine derivatives was studied with the substrates **85**, **130**, **154**, and **156–158** shown in Scheme 39. These substances were prepared from eremanthine (**1**) by simple standard procedures and were described in recent articles [168–170]. After exposure of these substrates to reaction conditions of inversion of the lactonic fusion, epimeric mixtures at C-6 were obtained in different proportions (Scheme 39). The variations in the proportions of products with *cis* lactonic fusion obtained in that work were attributed to steric effects at the hydroazulene system. A detailed discussion on the probable causes of variation in the proportions of products with *cis* lactonic fusion displayed in Scheme 39 was reported in a recent article and in its supplementary information [170]. The author would like to make a correction on the major product of the inversion reaction of lactonic fusion of the allylic acetate **156** (Scheme 39) previsously described in a congress abstract [167]. The major product obtained in that reaction is the allylic acetate **163** and not the allylic alcohol **162**

as it was written in an equivocal way in that abstract [167].

An intriguing result was obtained in the reaction of diol **140** with aqueous NaOH in refluxing DMF (Scheme 40). The product of this reaction was identified by ^{1}H NMR as a mixture of epimers **141** and **162** (3 : 1). After acetylation of this mixture with Ac_2O and pyridine, the major product **156** was separated and then used in reaction of inversion of the lactonic fusion (Scheme 39) [170]. The author would like to explain that the allylic acetate **156** was obtained for the first time in his works of scientific initiation [166] and *M.S.* [150] and not as it was previously described in an equivocal way [167]. It was reported in the congress abstract [167] that the substance **156** had been obtained in a work of *Ph.D.* [16], but the compound obtained in that *thesis* [16] was the diol **141** (Scheme 32). Reinvestigation of the methanol elimination on diol **140** using MeCN as the solvent of reaction resulted in generation of the epimeric mixture **141** and **162**. The major product of that reaction was the epimer **162** with *cis* lactonic fusion obtained in a proportion of (6 : 5) (^{1}H NMR) in relation to compound **141** (Scheme 40) [170]. The allylic alcohol **162** and its correspondent allylic acetate **163** possess the necessary structural requirements to unchain the rearrangements preconized by the hypothesis of the biotransformation of guaianolide into pseudoguaianolide (ambrosanolide) reported by Fischer et al. [14].

It was verified at the step of inversion of the lactonic fusion on isoeremanthine (**85**) that the use of concentrated solutions of that substrate in THF generated 6-*epi*-isoeremanthine (**159**) in mixture with a minor product identified by ^{1}H NMR as the compound **166** (5 : 1) (Scheme 41) [170]. The allylic alcohol **133**, was obtained when iodohydrin **139** was treated with zinc and acetic acid in refluxing EtOH (Scheme 42). The speculative mechanism of this reaction was published in a recent article [170].

6.12. Study of Catalytic Hydrogenation and Methanol Addition to α-Methylene-γ-Lactone of Eremanthine Derivatives. Besides the sequences of reactions described in the previous subitem (6.11), Alves [171] also studied the reactivity of allylic derivatives **127**, **128**, **133**, and **140** in catalytic hydrogenation reactions as well as the methanol addition to α-methylene-γ-lactone of iodohydrin **111** (Scheme 43). Catalytic hydrogenation of iodohydrin acetate **127** in EtOH with hydrogen and Pd-C yielded a single product identified by ^{1}H NMR as the allylic acetate **167**. On the other hand, catalytic hydrogenation of allylic alcohol **128** in EtOH with hydrogen and Pd-C furnished a complex mixture of substances. After a meticulous analysis of the ^{1}H NMR and ^{13}C NMR spectra, in combination with the calculations of molecular modeling, it was verified that the mixture obtained in the reaction was composed by intermediates that did not totally react and two products were resultant from hydrogenation of the reactive functions of the substrate **128**, characterized as the isomers **168** (major) and **169** (minor). Hydrogenation of allylic alcohol **133** afforded a mixture of products characterized by ^{1}H NMR as the compounds **170** and **171** (5 : 1) in mixture with traces of the lactones **172** and **173**. The stereochemistry of methyl groups C-14 and C-15 at the major product **170** was determined by NOE experiment. The catalytic hydrogenation reaction of allylic alcohol **140** using the catalyst Pt-C and low hydrogen pressure generated the compound **153** in quantitative yield. The treatment of iodohydrin **111** with a solution of NaOMe in methanol at room temperature furnished a single product characterized by ^{1}H NMR as the dimethoxylated compound **174**, as result of methanol addition to α-methylene-γ-lactone and nucleophilic substitution at C-15.

The catalytic hydrogenation of allylic alcohol **140** in mixture with its epimer at C-11 position (**175**), followed by the step of methanol elimination, generated a mixture of compounds **154** and **176** (Scheme 44). This result suggests that the addition of hydrogen to double bond C1-C10 on this mixture of allylic alcohols is induced by the group CH_2OMe at C-11 position. A detailed discussion on the reactivity of allylic derivatives from eremanthine shown in Schemes 43-44, in catalytic hydrogenation reaction, was presented in a recently published work including analysis of molecular modeling with the use of molecular mechanic tools (MM2 calculation) [171].

7. Conclusions

This review about the chemistry of eremanthine (**1**) has demonstrated the usefulness of the *chiron approach* to the syntheses of other sesquiterpene lactones derived from **1**, by the use of a building block with well-established stereocenters as starting material. From the described synthetic studies it was possible to know the reactivity of several functional groups at the compound **1** as well as in other derivatives obtained from **1**. Although the chemistry of eremanthine and its derivatives has been quite explored, there is still opportunity for new discoveries and syntheses of new substances by using this natural sesquiterpenoid as starting material.

Acknowledgments

J. C. F. Alves thanks FAPERJ and CNPq for the fellowships to develop the project "Chemical transformations of natural substances. I-Studies with eremanthine" [177], Professor Dr. Edna C. Fantini (in memoriam) for the supervision of the research project, and the Rural Federal University of Rio de Janeiro (UFRRJ) for the reception during the period in which the project was developed.

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[177] J. C. F. Alves would like to explain that the incorrectness previously committed in the writing of works about chemical transformations of eremanthine [150, 166–167] were, whenever possible, corrected and revised in works published on this decade [168–170].