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Article

Chemical Transformations of Eremanthine. Synthesis of Micheliolide and 1(R),10(R)-Dihydromicheliolide

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Eremantina (**1**), uma substância natural abundante, foi transformada em quatro etapas no diol **5**. Após hidrogenólise de **5** (55 psi de H_2, Pd/C, 30 min) obteve-se **7**. Hidrogenação de **5** usando-se uma baixa pressão de hidrogênio (5 psi) e um menor tempo de reação (15 min) forneceu uma mistura de **6** e **7** (3:1). Os compostos **6** e **7** foram, a seguir, transformados nas respectivas α-metileno-γ-lactonas miqueliolido (**9**) e 1(R),10(R)-diidromiqueliolido (**8**), após eliminação de metanol.

Eremanthine (**1**), an abundant natural substance, was transformed in four steps into diol **5**. Hydrogenolysis of **5** (55 psi of H_2, Pd/C, 30 min) furnished **7**. Hydrogenation of **5** using a low hydrogen pressure (5 psi) and a short reaction time (15 min) led to a mixture of **6** and **7** (3:1). Compounds **6** and **7** were then transformed respectively to the α-methylene-γ-lactones micheliolide (**9**) and 1(R),10(R)-dihydromicheliolide (**8**), after elimination of methanol.

Keywords: anticancer sesquiterpene lactones, eremanthine, micheliolide

Introduction

Sesquiterpene lactone is an important class of naturally occurring substances generally found in *Compositae* family.[1] Many of these compounds are endowed with an impressively rich spectrum of biological activity[2] as antileishmanial,[3] antifungal,[4] cytotoxic[5] and herbicide,[6] among others.[7] This diverse bioactivity of sesquiterpene lactones along with their structural complexity makes these compounds important targets for synthetic purposes.[8] Furthermore, with rare exceptions, their availability from natural sources is very limited. Therefore, it is important to sinthesize these compounds from easily available starting materials.

Eremanthine (**1**), a sesquiterpene lactone isolated from Brazilian compositae *Eremanthus elaeagnus*[9] and *Vanillosmopsis erythropappa*[10] is an inhibitor against infections caused by cercariae of *Schistosoma mansoni*. The abundance of this substance turned possible the obtention of others potentially active derivatives, as well as the synthesis of less abundant natural lactones, through chemical modifications of **1**.[11]

Continuing the research programme of chemical transformations of eremanthine (**1**), this compound was converted to the diol **5**,[12] a potential precursor for the synthesis of micheliolide (**9**), an anticancer sesquiterpene lactone isolated from *Michelia compressa*[13] and *Michelia champaca*.[14]

In this paper we report the obtention of diol **5** and its transformation into micheliolide (**9**) and 1(R),10(R)-dihydromicheliolide (**8**).

Results and Discussion

Initially, eremanthine (**1**) was transformed into diol **5** as outlined in Scheme 1 (conditions i - iv).[12]

The α-methylene-γ-lactone of eremanthine (**1**) was protected as methanol adduct **2**. The choice was due to the stability of this group and relative facility to be removed.[15] Thus, the reaction of eremanthine (**1**) with methanol catalysed by sodium methoxide furnished adduct **2** in nearly quantitative yield. Epoxidation of compound **2** with excess of peracetic acid solution in CH_2Cl_2 furnished diepoxide **3**[16] and crude product was submitted to ring opening through treatment with glacial acetic acid and equimolar amount of potassium iodide, in reflux of acetone. The use of equimolar amount of KI provided the chemoselective opening of the more reactive 4,15-α-epoxide through the nucleophilic attack of iodide at C_{15}.

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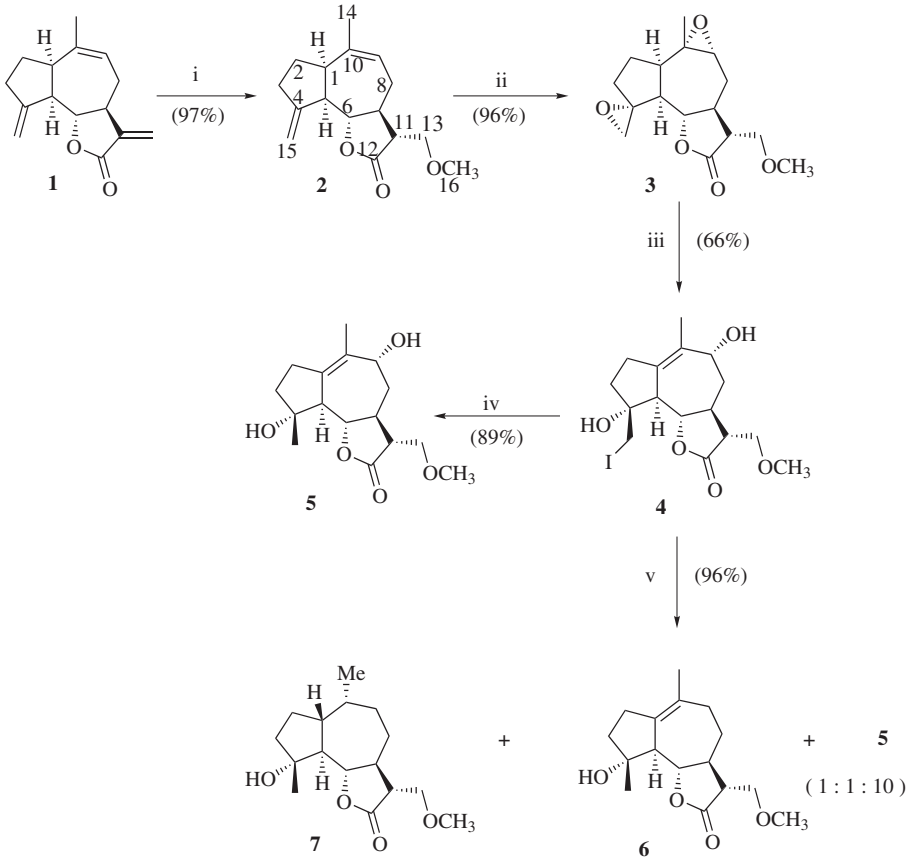


Scheme 1. Reagents and conditions: i) MeONa (0.4 equiv.) / MeOH (r.t. - 24 h); ii) AcO_2H / CH_2Cl_2 (r. t. - 48 h); iii) KI (1.1 equiv.); AcOH (15 equiv.) / Acetone (reflux - 11 h); iv) H_2 (45 psi); 10% Pd-C (0.1 equiv.), NaOAc (5.0 equiv.) / EtOH (r. t. - 3 h); v) H_2 (60 psi); 10% Pd-C (0.1 equiv.), NaOAc (5.0 equiv.) / EtOH (r. t. - 48 h).

On the other hand, the protonation of 9,10-α-epoxide contributed for the generation of a cationic intermediary at C_{10} where elimination of H^+ at C_1 furnished the compound **4**[17] in 66% yield after purification by flash chromatography. Hydrogenolysis of **4** with hydrogen catalysed by palladium on charcoal and mixture of sodium acetate and ethanol gave diol **5**.[12] At this point we decided to investigate this reaction more carefully in order to carry out the hydrogenolysis of C_{15}-I and C_9-OH in one step.

The classic literature of Organic Chemistry reports that hydrogenation of allylic alcohol with hydrogen and catalyst, for example palladium on charcoal, proceeds initially with hydrogenolysis of C-OH followed by reduction of double bond C-C.[18] In our case, the hydrogenation of tetrasubstituted double bond C_1-C_{10} at allylic alcohol **4** seemed to be an unfavourable reaction since tetrasubstituted olefins are more resistent and require higher temperatures and pressures.[19] This resistence is usually a function of increasing substitution and is presumably caused by steric factors.

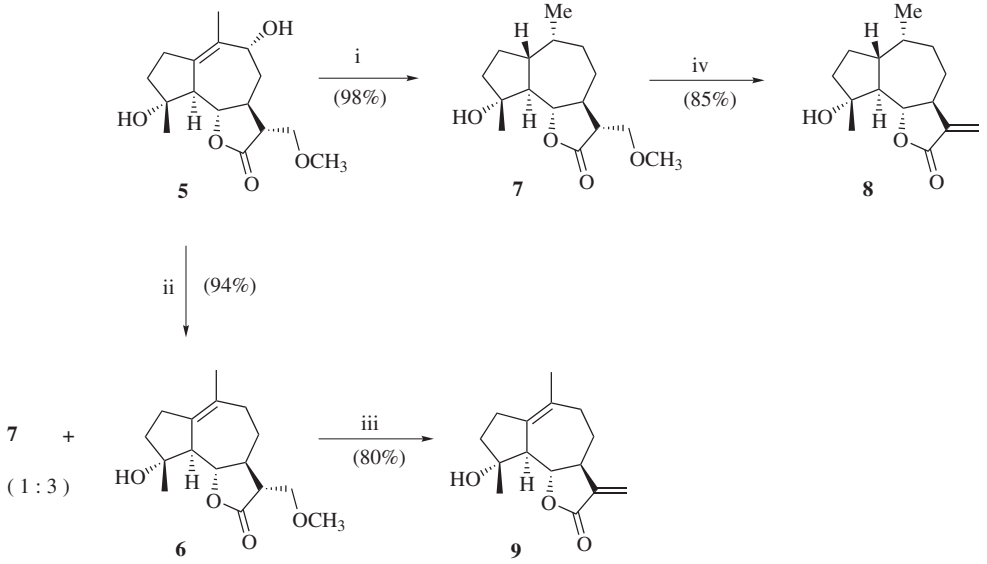
As we had observed before, the use of 45 psi of hydrogen pressure didn't cause any hydrogenolysis of C_9-OH at **4**. We planned to use a higher hydrogen pressure during several hours in order to convert **4** to **6** and an experiment was performed in which we used the highest recommended pressure for the Parr hydrogenation apparatus (condition v – Scheme 1).The reaction course was examined by TLC in regular times of one hour and after 48 h, two spots (Rf 0.29 and 0.6, EtOAc as eluent) were observed. The slow-eluting spot (R_f 0.29) corresponded to diol **5** by comparison with an authentic sample of this compound. On the other hand, the fast-eluting spot (R_f 0.6) seemed to correspond to the target molecule **6** due to its lower polarity. Because of the high polarity of compound **5**, we decided to extract the reaction products using two solvents of different polarities (ethyl ether and ethyl acetate) in order to separate the two fractions of R_f 0.29 and 0.6 by extraction. The crude product was partitioned first with ethyl ether and then exhaustively with ethyl acetate. After the usual aqueous work up and evaporation of the solvents, it was obtained two residues which were submitted to TLC. The spot of the ethereal residue corresponded to the product with R_f 0.6 and the residue of ethyl acetate to diol **5** (R_f 0.29). The ratio of diol **5** to product of R_f 0.6 was 5:1 and

96% global yield. In the ^{1}H NMR spectrum of the ethereal residue was observed the absence of the signals corresponding to H-9 (δ 4.22) and H-15 (δ 3.60 and δ 3.30), present in the spectrum of **4,** indicating thus the hydrogenolysis of C_9-OH and C_{15}-I bonds. The triplets at δ 3.99 and δ 3.79 (H-6 signals) and the singlets at δ 3.34 and δ 3.32 (H-16 signals) suggested the presence of two lactones (1 : 1 ratio by ^{1}H NMR). The methyl group attached to sp^2 carbon (H-14) was observed at δ 1.64. With these spectral data we concluded that spot of R_f 0.6 corresponded to two substances, where one of them was the compound **6**. A new TLC analysis of the ethereal residue (R_f 0.6) was performed using 35% EtOAc/hexane as eluent (elution repeated three times). After staining, it was observed two spots of very similar R_f. These results suggested that substance **6** had been formed and then transformed in part to another product in the reaction medium, maybe compound **7**. However the H-14 doublet of **7** was masked in the ^{1}H NMR spectrum of this mixture. To confirm the *in situ* conversion of **6** to **7**, we decided to perform the hydrogenolysis reaction using as starting material diol **5** (condition i – Scheme 2) in order to get **7** as a single product.

After reaction time the TLC revealed that diol **5** had been transformed to a single product of R_f 0.6 (eluent: 3 x 35% EtOAc/hexane). The ^{1}H NMR spectrum of product indicated hydrogenolysis of the C_9-OH bond besides reduction of double bond C_1-C_{10} at **5**. A doublet at δ 0.95 (3H, *J* 7.2 Hz) was attributed to H-14. One singlet at δ 3.32 (3H, H-16) and one triplet at δ 3.99 (1H, *J* 10.3 Hz, H-6) confirmed that **7** was the single product of this reaction. In the ^{13}C NMR spectrum was only observed one signal of sp^2 carbon (δ 175.9; C=O) confirming thus the hydrogenation of double bond C_1-C_{10}. The stereochemistry of the stereogenic carbons C_1 and C_{10} was determined by NOE experiment.[20] The *trans* junction between the five and seven-membered-rings of the hidroazulene system was confirmed by axial-axial coupling constants between H-5 and H-1 (*J* 11.2 Hz). The fast hydrogenation reaction of tetrasubstituted double bond C_1-C_{10} was an unexpected result since compound **2**, which has a trisubstituted double bond C_9-C_{10}, hydrogenated slowly [H_2 (60 psi); 10% Pd-C (0.1 equiv.); EtOH (r.t. – 4h)].[21]

Our attention was focused, at this stage, to examine the means for effecting only hydrogenolysis of the C_9-OH bond in **5**, in order to get compound **6,** the immediate precursor of micheliolide (**9**). After many experiments, we found that the best condition to carry out this reaction was the use of a low hydrogen pressure (5 psi) and a short reaction time (maximum of 15 minutes) (condition ii - Scheme 2). With this condition, the major product obtained was the compound **6**, as a mixture with **7** (94% yield, 3:1 ratio by ^{1}H NMR). The separation of **6** and **7** by column chromatography proved to be troublesome (practically identical R_{fs}) and to our delight, compound **6** could be crystallized from hexane.

Finally, restoration of α-methylene-γ-lactone function of compounds **6** and **7** was achieved using basic conditions.[15] The reactions were quenched with aqueous HCl in order to consume the excess of NaOH and lactonize the hydroxy acids formed in this stage. Micheliolide (**9**) and 1(R),10(R)-dihydromicheliolide (**8**) were obtained in 80% and 85% yield, respectively. Micheliolide (**9**) has



Scheme 2. Reagents and conditions: i) H_2 (55 psi); 10% Pd-C (0.1 equiv.); EtOH (r.t. - 30 min.); ii) H_2 (5 psi); 10% Pd-C (0.1 equiv.); EtOH (r.t. - 15 min.); iii) 4 mol L^{-1} NaOH (5.5 equiv.); DMF (reflux - 3 h); iv) 4 mol L^{-1} NaOH (5.5 equiv.); DMF (reflux - 2.5 h).

already been synthesized before by BF_3-mediated rearrangement of parthenolide.[22]

In conclusion, we have developed an efficient and straightforward synthesis (six steps) of micheliolide (**9**) (31% overall yield) and a new compound 1(R),10(R)-dihydromicheliolide (**8**) (45% overall yield) from the abundant natural product eremanthine (**1**), using inexpensive and easily available reagents. We expect that the synthesis outlined herein to be useful for the chemistry of sesquiterpene α-methylene-γ-lactones and related systems.

Experimental

Infrared spectra were recorded on a Perkin-Elmer 1420 spectrophotometer using either thin films on NaCl plates (film) or KBr discs (KBr). Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AC-200 (^{1}H : 200 MHz and ^{13}C : 50.3 MHz) spectrometer. $CDCl_3$ was used as the solvent, with Me_4Si (TMS) as internal standard. Coupling constants (*J*) are reported in Hz. Multiplicities are indicated as s (singlet), d (doublet), t (triplet), dd (doublet of a doublet), dt (double triplet), m (multiplet), bs (broad singlet), bd (broad doublet). ^{13}C multiplicities were assigned using a DEPT sequence. Mass spectra were obtained at 70 eV on a VG AutoSpecQ mass spectrometer. Chromatographic purifications were carried out with 230-400 mesh silica gel (flash chromatography). The eluent mixtures, used in the chromatographic separations, were prepared volume to volume (v/v) and are expressed in percentage (%). Thin layer chromatography was performed on aluminium sheets coated with 60 F_{254} silica. The TLC were revealed spraying with 2% $Ce(SO_4)_2$ in 2 mol L^{-1} H_2SO_4 and followed by heating. The melting points were taken on a Kofler apparatus and are uncorrected. Hydrogenations were carried out using a Parr apparatus.

*(11S)-Guaia-4(15),9-dieno-13-methoxy-12,6α-lactone, (**2**)*

A solution of sodium methoxide [sodium (0.040 g, 1.740 mmol) and methanol (7.5 mL)] was added to eremanthine (1) (1.000 g, 4.342 mmol) in methanol (19 mL). The mixture was stirred at room temperature for 24 h. Water (25 mL) was added and resulting mixture was concentrated in vacuo. An aqueous solution of 10% HCl (v/v) was added dropwise to residual mixture until pH 3. The mixture was transferred to a separatory funnel and then extracted with EtOAc (1 x 40 mL).The organic layer was separated and then washed with water (1 x 40 mL). The aqueous phases were extracted with EtOAc (2 x 40 mL) and the combined organic layers were dried (Na_2SO_4), filtered and evaporated to give **2** (1.105 g , 97% yield), as a brown oil. R_f 0.69 (50% EtOAc/hexane). IR (film) ν_{max} / cm^{-1} : 2920, 1775, 1660, 1440, 1320, 1180, 1100, 1005, 895. ^{1}H NMR ($CDCl_3$): δ1.40 – 1.70 (m, 2H); 1.78 (bs, 3H); 1.90 – 2.70 (m, 8H); 3.33 (s, 3H); 3.64 (d, *J* 4.4 Hz, 2H); 3.93 (t, *J* 9.6 Hz, 1H); 4.97 (bs, 1H); 5.15 (bs, 1H); 5.47 (bd, *J* 7.9 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 27.7 (CH_3); 29.2 (CH_2); 29.9 (CH_2); 30.1 (CH_2); 43.6 (CH); 46.9 (CH); 47.9 (CH); 51.7 (CH); 59.0 (CH_3); 68.8 (CH_2); 83.3 (CH); 110.3 (CH_2); 121.3 (CH); 137.7 (C); 150.2 (C); 175.8 (C=O).

*(11S)-4α,15α,9α,10α-Diepoxyguaia-13-methoxy-12,6α-lactone, (**3**)*

Preparation of peracetic acid solution. H_2O_2 (30% - 37 mL) was added to glacial acetic acid (37 mL) and the mixture was stirred for 30 minutes. CH_2Cl_2 (60 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 **2**.* Adduct **2** (1.000 g , 3.811 mmol) was dissolved in a solution of AcO_2H/CH_2Cl_2 (60 mL), prepared as described above. The resulting solution was kept in the dark and stirred at room temperature for 2 days. The solution was washed with water (2 x 40 mL), aqueous 5% $NaHCO_3$ (2 x 40 mL) and again with water (2 x 40 mL). The organic layer was separated and the aqueous phases were extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were dried (Na_2SO_4), filtered under activated charcoal and the solvent removed under reduced pressure to furnish diepoxide **3** as a colourless crystalline residue (1.077 g, 96% yield). R_f 0.29 (50% EtOAc/hexane). IR (KBr) ν_{max}/cm^{-1}: 2925, 1785, 1450, 1380, 1350, 1310, 1230, 1180, 1100, 1040, 880, 760. ^{1}H NMR ($CDCl_3$): δ 1.36 (s, 3H); 1.45 – 1.95 (m, 4H); 2.10 – 2.55 (m, 4H); 2.60 – 2.75 (m, 1H); 2.85 (d, *J* 4.2 Hz, 1H); 2.90 – 3.05 (m, 1H); 2.97 (d, *J* 5.2 Hz, 1H); 3.11 (d, *J* 4.2 Hz, 1H); 3.33 (s, 3H); 3.60 (m, 2H); 3.72 (dd, *J* 9.7 and 11.3 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 25.4 (CH_3); 26.0 (CH_2); 28.1 (CH_2); 28.8 (CH_2); 39.7 (CH); 44.8 (CH) ; 46.7 (CH); 49.7 (CH_2); 51.6 (CH); 58.9 (CH_3); 61.4 (CH); 62.8 (C); 65.8 (C); 69.0 (CH_2); 81.2 (CH); 175.2 (C=O).

*(11S)-Guai-1(10)-eno-4α,9α-dihydroxy-13-methoxy-15-iodine-12,6α-lactone, (**4**)*

A mixture of diepoxide **3** (1.050 g, 3.567 mmol), acetone (6.3 mL), glacial acetic acid (3.1 mL, 54.151 mmol) and KI (0.652 g, 3.927 mmol) was refluxed for 11 h. It was then allowed to cool, diluted with EtOAc (35 mL) and solution was washed with water (1 x 35 mL), aqueous 5% $NaHCO_3$ (2 x 35 mL), aqueous 5% $Na_2S_2O_3$ (1 x 35 mL) and again with water (1 x 35 mL). The organic layer was

separated and the aqueous phases were extracted with EtOAc (2 x 35 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to furnish a brownish crystaline residue which was purified by column chromatography (45% EtOAc/hexane) to yield **4** (0.996 g, 66% yield) as yellowish crystals [mp 109 °C (decomposition)]. R_f 0.11 (50% EtOAc/hexane). IR (KBr) ν_{max} / cm^{-1}: 3500, 2920, 1780, 1440, 1310, 1210, 1155, 1125, 1040. ^1H NMR ($CDCl_3$): δ 1.40 – 1.60 (m, 1H); 1.60 – 1.90 (m, 3H); 1.79 (bs, 3H); 2.00 – 2.55 (m, 5H); 2.80 – 3.05 (m, 1H); 3.15 – 3.40 (m, 1H); 3.30 (d, *J* 10.8 Hz, 1H); 3.35 (s, 3H); 3.60 (dd, *J* 2.2 and 10.8 Hz, 1H); 3.67 (d, *J* 4.2 Hz, 2H); 3.86 (t, *J* 10.3 Hz, 1H); 4.22 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 15.3 (CH_2); 22.5 (CH_3); 29.6 (CH_2); 33.9 (CH_2); 37.1 (CH_2); 39.8 (CH); 46.2 (CH); 55.3 (CH); 59.1 (CH_3); 68.2 (CH_2); 72.0 (CH); 80.8 (C); 82.6 (CH); 133.5 (C); 133.7 (C); 175.3 (C=O).

*(11S)-Guai-1(10)-eno-4α,9α-dihydroxy-13-methoxy-12,6α-lactone, (**5**)*

A mixture of compound **4** (0.300 g, 0.710 mmol), ethanol (9.0 mL), NaOAc (0.290 g, 3.535 mmol) and 10% Pd-C (0.075 g, 0.070 mmol) was shaken with hydrogen (45 psi) in a Parr apparatus for 3 h at room temperature. The reaction was filtered, water (20 mL) was added and the mixture was concentrated in vacuo. The residual product was diluted with EtOAc (20 mL) and then washed with water (20 mL), aqueous 5% $NaHCO_3$ (20 mL), aqueous 5% $Na_2S_2O_3$ (20 mL) and again with water (20 mL). The organic layer was separated and the aqueous phases were vigorously extracted with EtOAc (5 x 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated. Purification of the crystalline residue by silica gel column chromatography using 80% EtOAc/hexane gave diol **5** (0.187 g, 89% yield) as colourless crystals [mp 142-144 °C]. R_f 0.03 (50% EtOAc/hexane). IR (KBr) ν_{max} / cm^{-1}: 3500, 2930, 1760, 1445, 1200, 1140, 990. ^1H NMR ($CDCl_3$): δ 1.25 (s, 3H); 1.40 – 1.60 (m, 2H); 1.65 – 1.90 (m, 4H); 1.78 (bs, 3H); 2.05 – 2.35 (m, 2H); 2.44 (dt, *J* 4.2 and 14.4 Hz, 1H); 2.75 – 3.00 (m, 2H); 3.35 (s, 3H); 3.67 (d, *J* 4.2 Hz, 2H); 3.85 (t, *J* 10.3 Hz, 1H); 4.21 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 22.3 (CH_3); 22.4 (CH_3); 30.0 (CH_2); 34.0 (CH_2); 37.8 (CH_2); 39.5 (CH); 46.3 (CH); 57.0 (CH); 59.0 (CH_3); 68.3 (CH_2); 72.0 (CH); 80.0 (C); 83.4 (CH); 132.8 (C); 134.6 (C); 175.6 (C=O).

*(1R,10R,11S)-Guaia-4α-hydroxy-13-methoxy-12,6α-lactone, (**7**)*

Diol **5** (0.100 g, 0.337 mmol), ethanol (3.0 mL) and 10% Pd-C (0.036 g, 0.034 mmol) were shaken with hydrogen (55 psi) in a Parr apparatus for 30 min at room temperature. The mixture was filtered and evaporated to furnish a residual product, which was then filtered on silica gel (80% EtOAc/hexane). After evaporation under reduced pressure compound **7** (0.093 g, 98% yield) was obtained as colourless crystals [mp 84-85 °C]. R_f 0.41 (50% EtOAc/hexane). IR (KBr) ν_{max} / cm^{-1}: 3480, 2930, 1780, 1460, 1410, 1345, 1195, 1100, 1000. ^1H NMR ($CDCl_3$): δ 0.80 – 1.10 (m, 2H); 0.95 (d, *J* 7.2 Hz, 3H); 1.15 – 1.35 (m, 2H); 1.32 (s, 3H); 1.35 – 1.85 (m, 4H); 1.85 – 2.10 (m, 2H); 1.94 (dd, *J* 10.3 and 11.2 Hz, 1H); 2.16 (bs, 1H, OH, D_2O exchange); 2.25 – 2.50 (m, 2H); 3.32 (s, 3H); 3.64 (m, 2H); 3.99 (t, *J* 10.3 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 13.3 (CH_3); 24.4 (CH_2); 24.8 (CH_3); 26.0 (CH_2); 31.5 (CH_2); 31.9 (CH); 38.8 (CH_2); 43.7 (CH); 46.4 (CH); 48.4 (CH); 55.3 (CH); 59.2 (CH_3); 68.6 (CH_2); 80.0 (C); 83.9 (CH); 175.9 (C=O). *m/z* (%): 282 (M^+, 2%); 264 (100); 232 (25); 219 (14); 205 (22); 192 (51); 178 (80); 161 (42); 149 (52); 133 (40); 120 (82); 105 (50); 93 (55); 79 (60); 71 (72); 55 (86).

*(11S)-Guai-1(10)-eno-4α-hydroxy-13-methoxy-12,6α-lactone, (**6**)*

Diol **5** (0.050 g, 0.168 mmol), ethanol (1.5 mL), 10% Pd-C (0.018 g, 0.017 mmol) and hydrogen (5 psi) were shaken in a Parr apparatus at room temperature for 15 minutes. The mixture was filtered and concentrated in vacuo. Hexane (10 mL) was added to the crude product (0.045 g) and the mixture was heated to boil. The resulting cloudy solution was carefully separated from insoluble residual oil with a pipette and then transferred to a round-botton flask which was allowed at room temperature. After 24 h, it was observed crystalline agglomerates inside the solution. The liquid phase was separated and crystals were washed with hexane and then dried under reduced pressure. Compound **6** (0.020 g, 42% yield) was obtained as colourless crystals [mp 108-109 °C]. R_f 0.44 (50% EtOAc/hexane). IR (KBr) ν_{max} / cm^{-1}: 3590, 2940, 1775, 1445, 1385, 1205, 1180, 1110, 990. ^1H NMR ($CDCl_3$): δ 1.15 – 1.40 (m, 1H); 1.26 (s, 3H); 1.64 (d, *J* 1.5 Hz, 3H); 1.65 – 1.85 (m, 2H); 1.85 – 2.05 (m, 1H); 2.05 – 2.25 (m, 5H); 2.25 – 2.40 (m, 1H); 2.40 (dt, *J* 4.0 and 12.0 Hz, 1H); 2.64 (bd, *J* 10.1 Hz, 1H); 3.34 (s, 3H); 3.67 (m, 2H); 3.79 (t, *J* 10.1 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 22.5 (CH_3); 23.5 (CH_3); 26.8 (CH_2); 29.7 (CH_2); 34.9 (CH_2); 38.1 (CH_2); 47.7 (CH); 48.5 (CH); 57.8 (CH); 58.9 (CH_3); 68.1 (CH_2); 80.0 (C); 83.8 (CH); 131.0 (C); 131.5 (C); 175.4 (C=O). *m/z* (%): 280 (M^+, 22%); 262 (36); 230 (24); 222 (20); 204 (14); 190 (31); 177 (42); 159 (60); 146 (51); 131 (43); 118 (100); 105 (63); 91 (64); 79 (38); 67 (22); 55 (52).

*Micheliolide, (**9**)*

A solution of compound **6** (0.020 g, 0.071 mmol) in DMF (0.5 mL) and aqueous 4 mol L^{-1} NaOH (0.10 mL, 0.400 mmol) was refluxed for 3 h. After allowed to cool at room temperature, aqueous 10% HCl (v/v) was added dropwise until pH 3. EtOAc (20 mL) was added and solution was washed with H_2O (2 x 20 mL). The organic layer was separated and the aqueous phases were extracted with EtOAc (2 x 20 mL). The organic phases were dried (Na_2SO_4), filtered and then exhaustively evaporated under reduced pressure. The residual product was filtered on silica gel ($CHCl_3$) and concentrated to furnish **9** (0.014 g, 80% yield) as colourless crystals.[23] mp lit.[22]:142-145 °C; mp 131-133 °C. R_f 0.50 (50% EtOAc/hexane). IR (KBr) ν_{max} / cm^{-1}: 3550, 2930, 1765, 1670, 1450, 1410, 1375, 1260, 1155, 990, 950. ^1H NMR ($CDCl_3$): δ 1.15 – 1.45 (m, 1H); 1.28 (s, 3H); 1.66 (bs, 3H); 1.70 – 1.95 (m, 2H); 2.00 – 2.50 (m, 6H); 2.55 – 2.80 (m, 2H); 3.79 (t, *J* 10.0 Hz, 1H); 5.48 (d, *J* 3.3 Hz, 1H); 6.19 (d, *J* 3.3 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 22.7 (CH_3); 23.9 (CH_3); 25.7 (CH_2); 30.0 (CH_2); 34.9 (CH_2); 38.2 (CH_2); 49.5 (CH); 58.6 (CH); 80.2 (C); 84.4 (CH); 119.5 (CH_2); 130.8 (C); 131.8 (C); 138.7 (C); 169.7 (C=O). *m/z* (%): 248 (M^+, 23%); 230 (41); 215 (26); 202 (30); 190 (100); 175 (28); 159 (25); 145 (64); 131 (32); 119 (33); 105 (50); 91 (44); 79 (27); 67 (17); 53 (45).

*1(R),10(R) – Dihydromicheliolide, (**8**)*

A solution of compound **7** (0.020 g, 0.070 mmol) in DMF (0.5 mL) and aqueous 4 mol L^{-1} NaOH (0.10 mL, 0.400 mmol) was refluxed for 2.5 h. After allowed to cool at room temperature, aqueous 10% HCl (v/v) was added dropwise until pH 3. EtOAc (20 mL) was added and solution was washed with H_2O (2 x 20 mL). The organic layer was separated and the aqueous phases were extracted with EtOAc (2 x 20 mL). The organic phases were dried (Na_2SO_4), filtered and then exhaustively evaporated under reduced pressure. The residual product was filtered on silica gel ($CHCl_3$) and concentrated to furnish **8** (0.015 g, 85% yield) as colourless oil. R_f 0.50 (50% EtOAc/hexane). IR (film) ν_{max} / cm^{-1}: 3440, 2940, 1765, 1660, 1470, 1380, 1150, 1000. ^1H NMR ($CDCl_3$): δ 0.80 – 1.05 (m, 2H); 0.96 (d, *J* 7.2 Hz, 3H); 1.15 – 1.47 (m, 2H); 1.34 (s, 3H); 1.50 – 2.50 (m, 8H); 2.75 – 3.00 (m, 1H); 4.02 (t, *J* 10.2 Hz, 1H); 5.41 (d, *J* 3.5 Hz, 1H); 6.13 (d, *J* 3.5 Hz , 1H). ^{13}C NMR ($CDCl_3$): δ 12.5 (CH_3); 23.0 (CH_2); 25.0 (CH_3); 26.0 (CH_2); 31.0 (CH_2); 31.9 (CH); 38.7 (CH_2); 45.5 (CH); 47.5 (CH); 56.3 (CH); 80.0 (C); 83.2 (CH); 119.3 (CH_2); 140.4 (C); 169.9 (C=O).

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References

1. Fraga, B. M.; *Nat. Prod. Rep.* **1998**, *15*, 73; *Ibid.* **1999**, *16*, 21; *Ibid* **1999**, *16*, 711; *Ibid.* **2000**, *17*, 483; *Ibid.* **2001**, *18*, 650; *Ibid.* **2002**, *19*, 650; *Ibid*. **2003**, *20*, 392; *Ibid*. **2004**, *21*, 669.
2. Schmidt, T. J.; *Current Org. Chem.* **1999**, *3*, 577.
3. Satake, M.; Fuchino, H.; Koide, T.; Takahashi, M.; Sekita, S.; *Jpn Patent PCT Int. Appl. WO 01 58,888* ***2001*** (*CA 2001, 135: 180895 h*).
4. Vajs, V.; Todorovic, N.; Ristic, M.; Tesevic, V.; Todorovic, B.; Janackovic, P.; Marin, P.; Milosavljevic, S.; *Phytochemistry* **1999**, *52*, 383.
5. Harimaya, K.; Inayama, S.; *Heterocycles* **1990**, *30 (2, Spec. Issue)*, 993; Appendino, G.; Gariboldi, P.; Menichini, F.; *Fitoterapia* **1991**, *62,* 275.
6. Macias, F. A.; Galindo, J. C. G.; Molinillo, J. M. G.; Castellano, D.; Velasco, R. F.; Chinchilla, D.; *Pestic. Sci.* **1999**, *55*, 662.
7. Fischer, N. H.; Lu, T.; Cantrell, C. L.; Acosta, J. C.; Quijano, L.; Franzblau, S. G.; *Phytochemistry* **1998**, *49*, 559; Macias, F. A.; Galindo, J. C. G.; Massanet, G. M.; *Phytochemistry* **1992**, *31*, 1969; Giordano, O. S.; Pestchanker, M. J.; Guerreiro, E.; Saad, J. R.; Enriz, R. D.; Rodriguez, A. M.; Jauregui, E. A.; Gusman, J.; Maria, A. O. M.; Wendel, G. H.; *J. Med. Chem.* **1992**, *35*, 2452; Baker, P. M.; Fortes, C. C.; Fortes, E. C.; Gazzinelli, G.; Gilbert, B.; Lopes, J. N. C.; Pellegrino, J.; Tomassini, T. C. B.; Wichinewski, W.; *J. Pharm. Pharmac.* **1972**, *24*, 853.
8. Ando, M.; *Yuki Gozei Kagaku Kyokaishi* **1992**, *50*, 858 (*CA 1992, 117 : 251566 t*); Kuroda, C.; Inoue, S.; Kato, S.; Satoh, J. Y.; *J. Chem. Res. (S)* **1993**, *2*, 62; Asaoka, M.; Ohkubo, T.; Itahama, H.; Kosaka, T.; Takei, H.; *Tetrahedron* **1995**, *51,* 3115; Rubinger, M. M. M.; Mann, J.; *J. Chem. Res. (S)* **1999**, *7*, 454; Yuuya, S.; Hagiwara, H.; Suzuki, T.; Ando, M.; Yamada, A.; Suda, K.; Kataoka, T.; Nagai, K.; *J. Nat. Prod.* **1999**, *62*, 22.
9. Vichnewski, W.; Gilbert, B.; *Phytochemistry* **1972**, *11*, 2563.
10. Corbella, A.; Gariboldi, P.; Jommi, G.; Ferrari, G.; *Phytochemistry* **1974**, *13*, 459; Lima, P. D. D. B.; *M.Sc. Dissertation*, NPPN, Universidade Federal do Rio de Janeiro, Brazil, 1983.

11. Maçaira, L. A.; Garcia, M.; Rabi, J. A.; *J. Org. Chem.* **1977**, *42*, 4207; Rabi, J. A.; Garcia, M.; Maçaira, L. A.; Machado, F. W. L.; *An. Acad. Bras. Cienc.* **1977**, *49*, 563; Garcia, M.; Machado, F. W. L.; Maçaira, L. A.; Rabi, J. A.; *Tetrahedron Lett.* **1980**, *21*, 777; Silva, A. J. R.; Garcia, M.; Baker, P. M.; Rabi, J. A.; *Org. Magn. Res.* **1981**, *16*, 230; Fantini, E. C.; Ferreira, J. L. P.; Rabi, J. A.; *J. Chem. Res. (S)* **1986**, 298.
12. Fantini, E. C.; *PhD Thesis*, Universidade Federal do Rio de Janeiro, Brazil, 1985.
13. Ogura, M.; Cordell, G. A.; Farnsworth, N. R.; *Phytochemistry* **1978**, *17*, 957.
14. Sethi, V. K.; Thappa, R. K.; Dhar, K. L.; Atal, C. K.; *Planta Med.* **1984**, *50*, 364.
15. Fantini, E. C.; Rabi, J. A.; *Cienc. Cult.* **1983**, *35 (7 Supl.)*, 403 (49-D.2.3).
16. Diepoxide **3** was prepared according to the procedure described for the synthesis of 9,10-α-4,15-α-diepoxy-eremanthine by : Ferreira, J. L. P.; *M.Sc. Dissertation*, NPPN, Universidade Federal do Rio de Janeiro, Brazil, 1985.
17. Compound **4** was prepared using the same procedure described for the ring opening of epoxide 9,10-α-4,15-α-diepoxy-eremanthine by : Fantini, E. C.; Ferreira, J. L. P.; Rabi, J. A.; *J. Chem. Res. (S)* **1986**, 298.
18. House, H. O.; *Modern Synthetic Reactions*, 2nd ed., W. A. Benjamin, INC.: Menlo Park, California, 1972, p. 23.
19. March, J.; *Advanced Organic Chemistry,* 3th ed., John Wiley & Sons: New York, 1985, p. 693.
20. The stereochemistry of methyl group at C-10 was established by NOE experiment. Irradiation of C-14 methyl group at δ 0.95 showed an enhancement of H-7 signal at δ 2.35 (3%) and an enhancement of H-5 signal at δ 1.94 (8%), indicating that methyl is in α-position.
21. Alves, J. C. F.; *M.Sc. Dissertation*, Universidade Federal Rural do Rio de Janeiro, Brazil, 1993.
22. Acosta, J. C.; Fischer, N. H.; Vargas, D.; *J. Nat. Prod.* **1993**, *56*, 90.
23. Crystallography data of micheliolide were reported by: Acosta, J. C.; Fronczek, F. R.; Fischer, N. H.; *Acta Cryst.* **1991**, C *47*, 2702.

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