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The *Journal of the Mexican Chemical Society* (former *Revista de la Sociedad Química de México*) is a peer reviewed trimonthly journal which publishes original contributions and critical reviews in all areas of chemical sciences. It will publish fundamental work on physical, organic, inorganic, theoretical, analytical and biological chemistry, as well as aspects of supramolecular chemistry, electrochemistry, polymer chemistry, natural products chemistry, oil chemistry, organometallic chemistry, medical chemistry, biochemistry, chemical ecology, green chemistry, environmental chemistry, macromolecular chemistry, nuclear chemistry, chemistry of materials, and catalysis, among other topics. Full detailes on how to submit material to publication are given in Instructions for Authors on the printed journal, on the website: www.jmcs.org.mx or via e-mail to: editor. jmcs@gmail.com

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The *Sociedad Química de México* was founded in 1956 as a non-profit association to promote the development of the professionals and students of chemistry in education, research, services and industry, and for the diffusion of chemical knowledge. The *Sociedad Química de México* organizes annually the *Mexican Congress of Chemistry* and the *National Congress of Chemical Education*, both congresses include activities of current interest for professionals and students of the chemical sciences. It grants annually the *"Andrés Manuel del Río*" National Award *of Chemistry* in the Academic area (field of research and field of education) and in the Technological area (field of technological development). It also grants each year the *Rafael Illescas Frisbie Best Bachelor, Master and Doctoral Thesis in Chemical Sciences Awards* and the biennial A*ward of the Sociedad Química de México in honor of the Doctor Mario J. Molina, directed to the professionals in Chemistry Sciences*.

The *Journal of the Mexican Chemical Society* (*J. Mex. Chem. Soc*) is the official journal of the *Sociedad Química de México*, it was published as *Revista de la Sociedad Químca de Méixico* (*Rev. Soc. Quím. Mex.*) from 1957 to 2003, changing its name in 2004. The *Journal of the Mexican Chemical Society* is a quarterly publication, devoted to the advancement of the understanding of chemistry by means of publication of research papers and critical reviews; the instructions for authors appear in each issue. The *Sociedad Química de México* also publishes since 2007 articles of general interest in the *Boletín de la Sociedad Química de México*.

La *Sociedad Química de México* fue fundada en 1956 como una agrupación sin fines de lucro para promover el desarrollo de los profesionales y estudiantes de la química en las áreas educativa, investigación, servicios e industria, y para difundir el conocimiento de la química. La *Sociedad Química de México* organiza anualmente el *Congreso Mexicano de Química* y el *Congreso Nacional de Educación Química*, en los cuales se desarrollan diversas actividades de interés para los profesionales y estudiantes de las ciencias químicas. Asimismo, otorga anualmente el *Premio Nacional de Química "Andrés Manuel del Río"* en el área Académica (campos de docencia e investigación) y en el área Tecnológica (campo de Desarrollo Tecnológico). También otorga anualmente el *Premio a las Mejores Tesis de Licenciatura, Maestría y Doctorado en Ciencias Químicas, Rafael Illescas Frisbie*. De manera bienal otorga el *Premio de la Sociedad Química de México en Honor al Doctor Mario J. Molina, dirigido a los profesionistas de las Ciencias Químicas*.

El *Journal of the Mexican Chemical Society* (*J. Mex. Chem. Soc.)*, es la revista oficial de la *Sociedad Química de México*. Desde 1957 y hasta 2003 fue publicada como *Revista de la Sociedad Química de México* (*Rev. Soc. Quím. Mex.*), cambiando su nombre en 2004. Es una publicación trimestral que tiene como objetivo coadyuvar al avance del entendimiento de la química; las instrucciones para los autores aparecen en cada fascículo. La *Sociedad Química de México* también publica desde 2007 artículos de interés general en el *Boletín de la Sociedad Química de México*.

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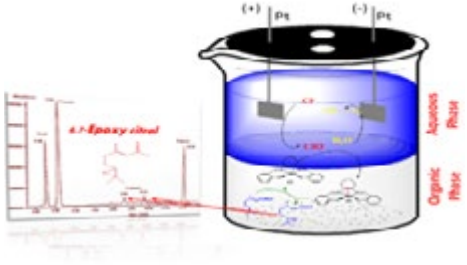

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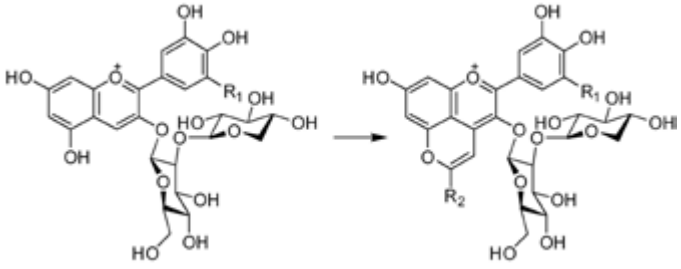

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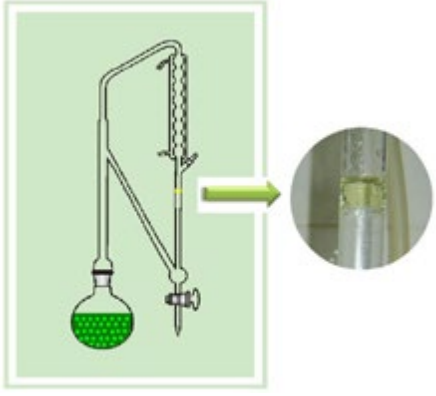

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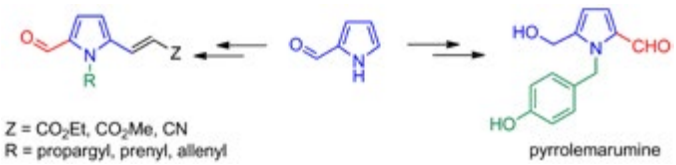

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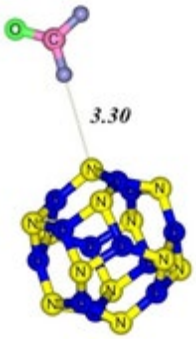

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The consolidation and international positioning of the *Journal of the Mexican Chemical Society* represents an important challenge in this globalized world. This is especially relevant with open access scientific journals arising from different parts of the planet, the increasing number of articles submitted for publication to our journal and the limited financial supports. These tasks demand continuous and different editorial adjustments that are being undertaken with the collaboration and enthusiastic support of the editorial board members. The increase in our impact index (JCR, july 2015) from 0.55 (2013) to 0.619 (2015) is a result of intense collaborative work and motivation to enhance the international positioning of the *Journal of the Mexican Chemical Society*.

Unfortunately, different problems experienced with the sponsor CONACYT (the National Council for Science and Technology) have delayed the incorporation of the journal into the automated electronic platform (Open Journal System) for its administration and production. We are working with the Editorial Board to achieve this task before the year's end.

I would like to take this opportunity to acknowledge the important and generous labor of associate editors and referees collaborating with the journal. We will continue our efforts to provide the best service to the chemical community.

Finally, on behalf of the Editorial Board, I renew the invitation to our colleagues from Mexico and abroad to consider the *Journal of the Mexican Chemical Society* as the preferred choice for publishing the results of your research.

Ignacio González
Editor

Article

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Epoxidation of Neral/Geranial Using a Jacobsen-Katsuki Mn catalyst by Chemical and Electrochemical Methods

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Abstract. In this study, *trans-(±)-N,N′*-bis(salicylidene)-1,2-cyclohexanediaminemanganese(III) chloride ([Mn(*t*-salcn)]Cl) was synthesized and used as a catalyst for the epoxidation of citral. The percentage of converted citral in two methods, chemical and electrochemical, was determined and compared; in the former method, the oxidizing agent NaClO was directly and completely added at the start of the reaction, while in the latter, ClO^- was progressively generated in situ. The reaction was monitored by the quantification of citral using gas chromatography coupled to mass spectrometry. The results showed that in both cases, the major products correspond to epoxides from citral isomers, although differences were observed in the value of percentage of epoxides obtained, besides the generation of side reactions affecting the yield of the product of interest.
Key words: Epoxidation; Electrochemical synthesis; Citral; Neral; Geranial.

Resumen. En este estudio se sintetizó el compuesto cloruro de *trans*-(±)-*N,N'*-bis(salicilideno)-1,2-ciclohexanodiaminomanganeso(III) ([Mn(*t*-salcn)]Cl) y se empleó como catalizador en la reacción de epoxidación de citral. Se determinó el porcentaje de conversión de citral al adicionar directa y completamente hipoclorito de sodio como agente oxidante desde el comienzo de la reacción y se comparó con el porcentaje de reacción de citral con el mismo agente oxidante generado progresivamente in-situ a través de un proceso electroquímico. El seguimiento de la reacción se realizó mediante la cuantificación de citral por cromatografía de gases acoplada a espectrometría de masas. Los resultados mostraron que en ambos casos los productos mayoritarios corresponden a epóxidos de los isómeros de citral, pero se encontraron diferencias en el valor de los porcentajes de epóxidos obtenidos, además de la generación de reacciones secundarias que afectan el rendimiento del producto de interés.
Palabras Clave: Epoxidación; Síntesis electroquímica; Citral; Neral; Geranial

Introduction

Epoxides are organic compounds of significance in fine organic synthesis; they are used as precursors to obtain molecules of biochemical interest. The 6,7-epoxide of citral is utilized for the synthesis of 1,2-epoxy-carotenoides such as 1,2-epoxy-lycopene and 1,2,1′,2′-diepoxy-lycopene [1], which are well-known antioxidants and inflammatory mediators; it is also utilized for the synthesis of complex heterocyclic derivatives, which have permitted mechanistic investigation of reactions involving carbocations [2]. In addition, the 2,3-epoxide of the same compound is an important precursor for the synthesis of different benzofurans of interest, due to the biological activity of its derivatives [3]. Different reactions have been employed for the generation of epoxides [4,5], and studies have been ongoing with the aim of improving the yield and enantioselectivity of reactions [6-8].

Typically, epoxidation is conducted using a catalyst, which modifies the rate of reaction as well as controls the intensity and the selectivity of oxidation. Jacobsen [9] reported one of the most representative studies on the epoxidation of olefins [9], in which the Schiff's base *N,N′*-bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediamine and manganese(III) was used as precursor of the complex *N,N′*-bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride, known as Jacobsen's catalyst. This catalyst and those of its type contain a Mn^{3+} metallic center, which is oxidized to Mn^{5+} at activation. Activation is performed by the addition of an oxidizing agent. For some widely studied epoxidation reactions with the use of Jacobsen-type catalysts [5,10-12], a high conversion percentage, as well as enantiomeric excess, has been reported.

Most of the abovementioned synthetic routes to epoxides involve a direct chemical reaction between the substrate and catalyst, which has been previously activated by an oxidizing agent added from the start into the reaction container. However, the oxidizing agent can compete with the catalyst for the substrate, thereby generating products with a degree of oxidation higher than that required for the epoxides.

In recent years, biphasic chemical and electrochemical systems have been employed [13,14], affording products of greater purity. Biphasic systems allow for the use of catalysts with low or null solubility in water, given that the activation of the catalyst possibly occurs at the interface between water and the organic solvent. In addition, in biphasic electrochemical systems, it is possible to control the amount of oxidizing agent and the rate at which it is added to the system so as to improve the percentage conversion as well as the selectivity of epoxidation. These systems permit the use of oxidizing agents that are soluble in water and insoluble in organic solvents, where direct contact between the oxidizing agent and the substrate is decreased.

The conventional oxidizing agents used in epoxidation are sodium hypochlorite [12], dimethyldioxirane [15, 16], iodosylbenzene [17, 18], and hydrogen peroxide [19, 20]; nevertheless, hypochlorite (ClO^-) is most commonly used because of its high percentage of active oxygen [21]. Jacobsen [12] and Meunier [22] have independently used ClO^- for the epoxidation of *cis*-β-methyl styrene and epoxidation of cyclohexane, respectively. The reaction between ClO^- and the catalyst involves the oxidation of the metallic center from Mn(III) to Mn(V) and the consequent reduction from ClO^- to Cl^-. The olefin substrate forms an epoxide, while the oxidized catalyst returns back to Mn(III) [23]. For epoxidation by the classical chemical method and using biphasic systems, ClO^- is completely added to the aqueous phase at the start of the reaction and remains in contact with the catalyst and substrate at the interface. Hence, reactions typically occur directly between the oxidant and substrate, generating undesired products (especially alcohols and/or aldehydes); these products decrease the yield of epoxide.

For electrochemical epoxidation in biphasic systems, ClO^- is electrochemically generated in the aqueous phase by the oxidation of Cl^- on the surface of a platinum electrode. The electrogenerated ClO^- migrates to the interface and activates the catalyst dissolved in the organic phase by the oxidation of its metallic center, while ClO^- is reduced again to Cl^-. Then, the substrate, also dissolved in the organic phase, forms an epoxide with the activated catalyst, while the catalyst returns to its original oxidation state (Fig. 1). Nevertheless, in this case, direct contact between ClO^- and the substrate can also occur at the interface and affect the yield and purity of the product, in the same manner as in the chemical process.

The principal difference between the chemical and electrochemical processes lies in the control of the rate of the addition of the oxidizing agent when it is generated electrochemically, and consequently in the lower ClO^- concentration at the interface as compared to the scenario observed in the chemical process. Because of this difference in the concentrations of ClO^- in the aqueous phase, and hence at the interface, it is imperative to establish the preference of the hypochlorite to react with the catalyst or with the substrate in the chemical and electrochemical reactions.

The electrochemical generation of the oxidizing agent in aqueous media is a methodology that contributes to reduce the use of auxiliary substances and toxic solvents. It also allows the atomic saving due to the fact that the amount of produced

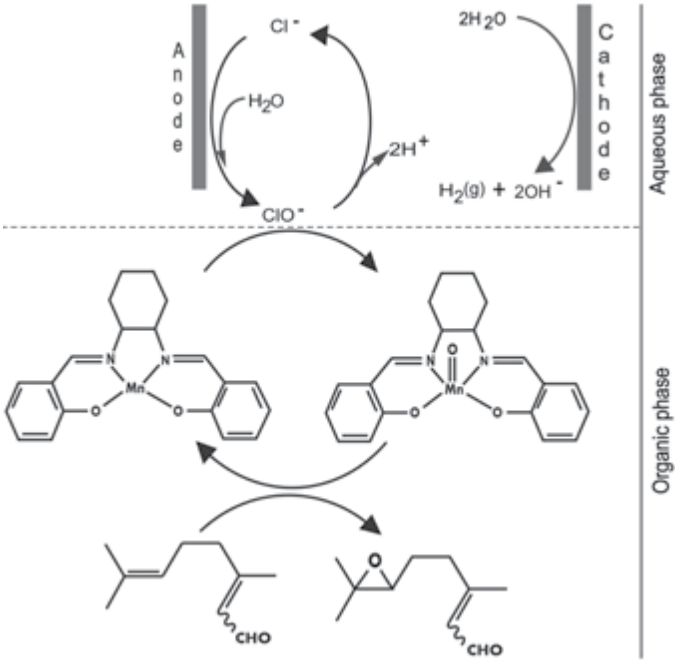


Fig. 1. Representation of electrochemical epoxidation mechanism in a biphasic system.

substance is just that required by chemical reaction. The reduction of number and quantity of residues is an additional benefit. Due to all these aspects, the electrochemical methods are considered an important tool for development of green chemistry [24, 25].

To determine the effect of the oxidizing agent on the percentage conversion in both chemical and electrochemical epoxidation, herein, we compared the performance of the epoxidation of citral using the *trans*-(±)-*N,N′*-bis(salicylidene)-1,2-cyclohexanediaminemanganese(III) chloride, a [M(*t*-salcn)]Cl-type catalyst, and the electrochemical generation of the oxidizing agent ClO^- utilized for catalyst activation, with the epoxidation of citral using the same catalyst, activated by the direct and complete addition of ClO^- from the start of the reaction. In both processes, biphasic systems were used. The aforementioned *trans*-(±)-*N,N′*-bis(salicylidene)-1,2-cyclohexanediamine manganese(III) chloride catalyst was synthesized by the electrochemical method via the reaction between Mn(III) and the *trans*-(±)-*N,N′*-bis(salicylidene)-1,2-cyclohexanediamine (H_2*t*-salcn) ligand, which was also synthesized in our laboratory.

In this study, the enantioselectivity of catalyst was not determined because the main purpose of the work was to establish the difficulties and advantages when electrochemical method is used to generate the oxidant agent in controlled form, respect to addition of the same oxidant agent like salt at the start of the reaction.

In this study, the substrate citral ($C_{10}H_{16}O$) or 3,7-dimethyl-2,6-octadienal is a mixture of two monoterpene aldehydes: geranial and neral. Geranial (2-*(E)*-3,7-dimethyl-2,6-octadienal) is the *trans* isomer, while neral (2-*(Z)*-3,7-dimethyl-2,6-octadienal) is the *cis* isomer [26, 27]. Citral is a natural

compound with significant potential in the pharmaceutical and chemical industries given its broad applications ranging from the generation of citric flavors and aromas to the synthesis of organic macromolecules [28-31]. The essential oil of *Cymbopogon citratus* is one of the main natural sources of citral, which is known as lemongrass or "limonaria," in South America; it is an aromatic plant with broad global distribution, belonging to the family of Gramineae, with traditional therapeutic uses [32, 33].

Results and discussion

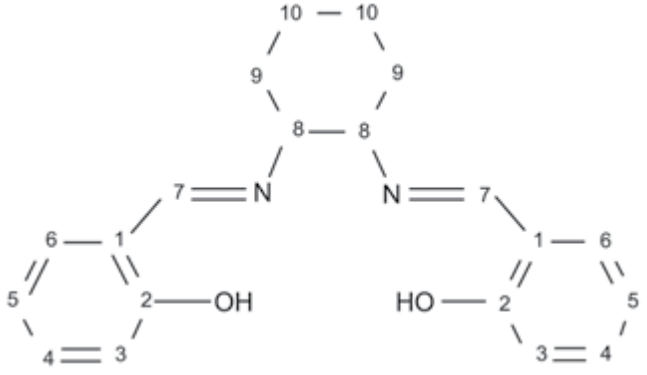
Synthesis and characterization of the H_2*t*-salcn ligand

The H_2*t*-salcn Schiff's base was obtained in 95% yield; it is not a conductor and is not soluble in water, but it is slightly soluble in non-polar chlorinated solvents such as dichloromethane and aromatic solvents such as toluene. Spectroscopic characterization via UV-Vis, FTIR, ^{1}HNMR, and ^{13}C NMR confirmed that the structure of the compound obtained corresponds to the expected ligand (structure 1).

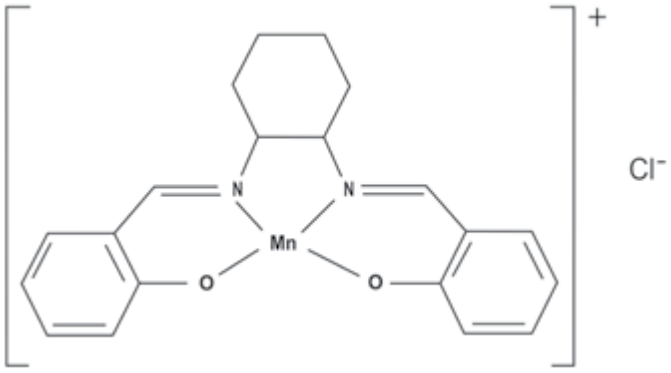
Electrosynthesis and characterization of the [Mn(*t*-salcn)]Cl complex

The yield of the complex synthesized at room temperature was 88.0%. The compound obtained was a 1:1-type electrolyte, indicating that Cl^- is outside the coordination sphere of manganese; moreover, it is soluble in chloroform, DMSO, and DMF, albeit with low solubility in water. Elemental analysis confirmed the general formula to be $C_{20}H_{20}N_2O_2MnCl$ (structure 2) without coordinated water. The percentage of chloride was obtained by potentiometric evaluation with $AgNO_3$, the percentage of Mn was obtained by atomic absorption spectrophotometry, and the percentage of oxygen was determined by difference.

The coordination of the ligand to manganese(III) was confirmed by FTIR spectroscopy, as evidenced by the variation in the absorption frequency of the C=N group of the ligand and



Structure 1. *Trans*-(±)-*N,N*′-bis(salicylidene)-1,2-cyclohexanediamine (H_2*t*-salcn) ligand.



Structure 2. *Trans*-(±)-*N,N*′-bis(salicylidene)-1,2-cyclohexanediamine-manganese (III) chloride ([Mn(*t*-salcn)]Cl).

the off-plane vibration of the C–O bond. In addition, an anodic peak (-95 mV) and a cathodic peak (-265 mV) were observed in the cyclic voltammogram of the complex dissolved in MeCN with 0.1 M tetrabutylammonium perchlorate using a mercury drop electrode (Fig. 2), both characteristic of the complex, which were not observed for the ligand or metal. The quasi-reversible electrochemical signals are attributed to equilibrium between $[Mn^{II}\text{-salcn}]^0$ and $[Mn^{III}\text{-salcn}]^+$, in analog form to showed by Horwitz and co-workers [34].

Chemical epoxidation

The chemical process was examined by gas chromatography; with the increase in the concentration of the catalyst in the reaction system, the disappearance of citral progressively increased until it reached a value close to 77% with 5 mol% catalyst (Fig. 3). Moreover, with the increase in the catalyst concentration to 15 mol%, the rate of disappearance of the starting material slightly increased to 83%. Considering these results, a catalyst concentration of 5 mol% was employed in subsequent experiments.

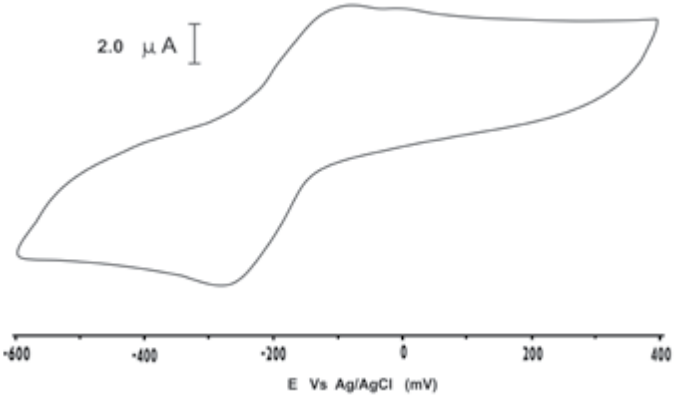


Fig. 2. Cyclic voltammetry for [Mn(*t*-salcn)]Cl complex dissolved in MeCN with 0.1 M tetrabutylammonium perchlorate at mercury drop electrode. Scan rate 100 mV/s.

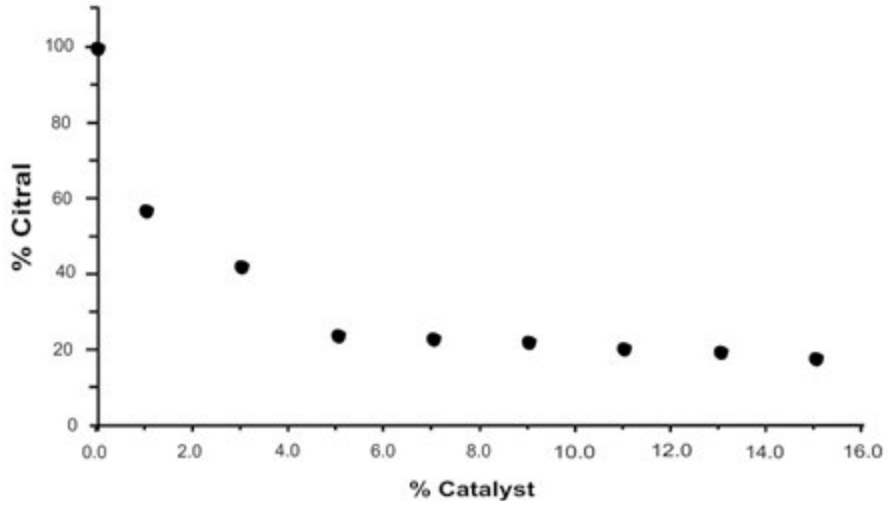


Fig. 3. Variation of the reaction percentage of citral as a function of catalyst concentration. Reaction time 8 h.

The percentage of the disappearance of citral reported was calculated after the subtraction of the loss of this substrate by volatilization at each stage during the progress of the experiment, which amounted to 14%. Moreover, after 4 h of the addition of the oxidizing agent, citral reaction percentage values reached 36%. Furthermore, at 8 h, the substrate conversion reached a maximum of 68%, and between 8 and 16 h, this percentage only increased marginally by 1%.

Fig. 4 shows the effect of the oxidizing agent with time; results obtained indicated that with the decrease in the concentration of ClO^- in the system, only one tenth of its initial value was reached at 8 h (Fig. 4). Taking into account that at 8 h, the conversion of citral reached only 68% and that the initial ClO^- concentration was stoichiometrically equivalent to that of citral, a less-pronounced decrease for the ClO^- content in the solution would be expected. Nevertheless, ClO^- was notably consumed more rapidly than the substrate, which implies that the oxidant is consumed. This result suggest that ClO- active the catalyst, but also directly reacts with citral or participates in secondary reactions possibly involving catalyst degradation.

Electrochemical epoxidation

Electrochemical generation of hypochlorite

The electrochemical generation of ClO^- from sodium chloride was carry out applying a current density of 20 mA/cm^2, the initial and final potential values were 2.2 and 2.4 V respectively during eight hours. The process was monitored in the same manner as for the chemical method. Initially, ClO^- generated was evaluated in a blank cell, that is, without the presence of the catalyst and without citral. Thereafter, ClO^- from the

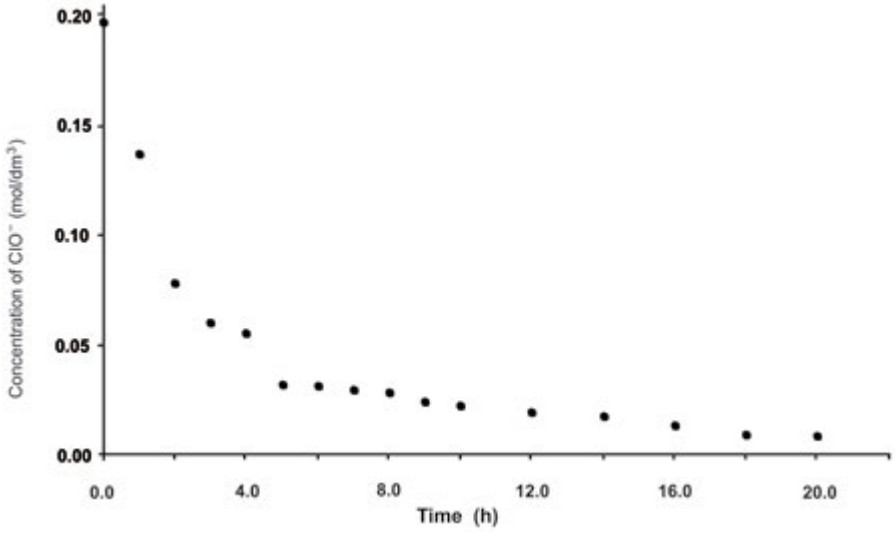


Fig. 4. Variation of the ClO^- concentration as a function of the epoxidation time for citral by the chemical method.

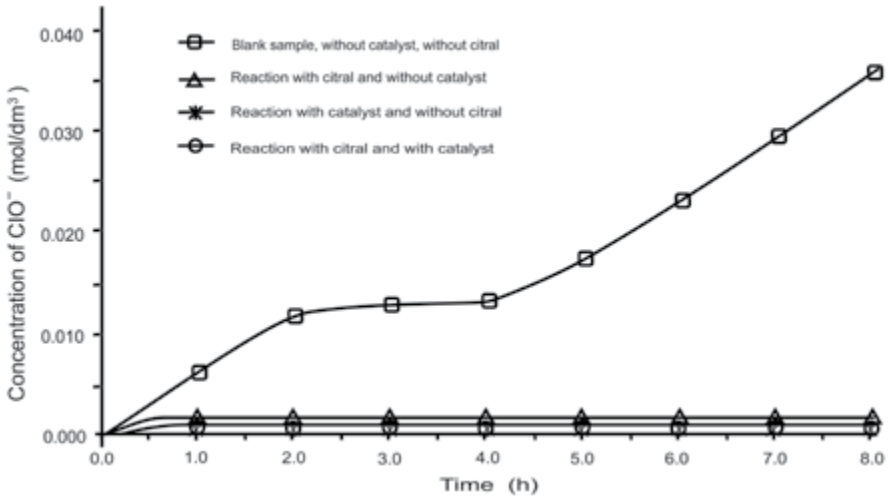


Fig. 5. Determination of hypochlorite generated during electrochemical epoxidation at 20 mA/cm^2 in the presence and absence of each component.

solution containing citral, and not the catalyst, was titrated. Third, ClO^- from the solution containing the catalyst but not citral was evaluated, and finally, ClO^- was titrated in the solution containing citral and catalyst at concentrations mentioned in the experimental section. The results obtained (Fig. 5) confirm the generation of ClO^- in the electrochemical cell, also indicating its increased concentration in the blank cell, as a function of time. For the cell with the catalyst, the electrogenerated ClO^- was completely and immediately consumed, indicating that the oxidizing agent reacts with the catalyst as expected; however, because the activated catalyst was not being used up (absence of substrate), the rate of disappearance of ClO^- would be expected to not be as high as that observed during titration. At this stage, it was not possible to verify whether the reaction between both species was as expected, that is, the oxidation of the metallic center of the catalyst and generation of chloride from hypochlorite. ClO^- also rapidly disappeared in the cell containing citral but not containing the catalyst, indicating that the substrate is directly oxidized by the oxidizing agent without catalyst mediation. Finally, upon assessing ClO^- generated in the cell containing citral and catalyst in the organic phase, the oxidizing agent immediately disappeared, confirming that hypochlorite rapidly reacts with both catalyst and substrate. Fig. 5 shows the evaluation curves for each of the cells previously described.

From the results obtained by the electrochemical method, a greater decrease of the substrate concentration at a reaction time of 4 h was observed as compared to that observed for the chemical method, with a citral reaction percentage of 42%. Moreover, at time greater than 4 h, the increase observed was less than 4%, which was attributed to the passivation observed on both electrodes as well as catalyst inactivation.

Electrode passivation observed at a reaction time greater than 4 h was attributed to the presence of an oily film, which was not observed in systems without the catalyst; thus, the oily film is attributed to the deposition of the catalyst or degradation products of the catalyst generated by reaction with ClO^-. From the aforementioned result, it is inferred that the catalyst is transferred from the organic phase to the aqueous phase. The presence of the catalyst in the aqueous phase was confirmed by UV-Vis spectroscopy: three well-defined absorption signals were observed, which disappear on the addition of ClO^-. The partial loss of the catalyst means that there is less chance of reaction with citral as well as the passivation of the electrodes, resulting in the restriction or obstruction of the oxidation from Cl^- to ClO^-.

The oily film deposited on the electrodes is possibly generated by the irreversible formation of μ-oxo-manganese(IV) inactive dimeric films on the anode of the cell, associated with the oxidation of the metallic nucleus of the catalyst, and likewise, to that generated in the C=N double bond of the organic ligand used in the complex, attributed to the use of oxidizing agents such as ClO^- [16], which could be responsible for the rapid disappearance of ClO^- in the cells containing only the catalyst.

Gas Chromatography–Mass Spectrometry Analysis

After 4 h of the reaction, the products generated from electrochemical epoxidation in the presence of the catalyst were extracted with hexane. Fig. 6 shows the chromatogram obtained from the analysis of the extract by gas chromatography coupled to mass spectrometry. The most intense signals were observed at 4.0 and 5.5 min, corresponding to neral and geranial isomers, respectively. To establish the citral reaction percentage, the sum of the areas of both isomers after the reaction time was determined and compared to the same sum of areas at zero reaction time, subtracting the loss of material during the different steps of the process. The following signal intensity is the internal pattern signal (eugenol), which appeared at 12.10 min. Signals were observed at 8.66 and 9.76 min, corresponding to the major products in the reaction; these signals appeared with an area significantly smaller than expected, given that material loss occurred during the extraction of the reaction products in case of citral isomers. For citral, such loss increased to 14%, while for

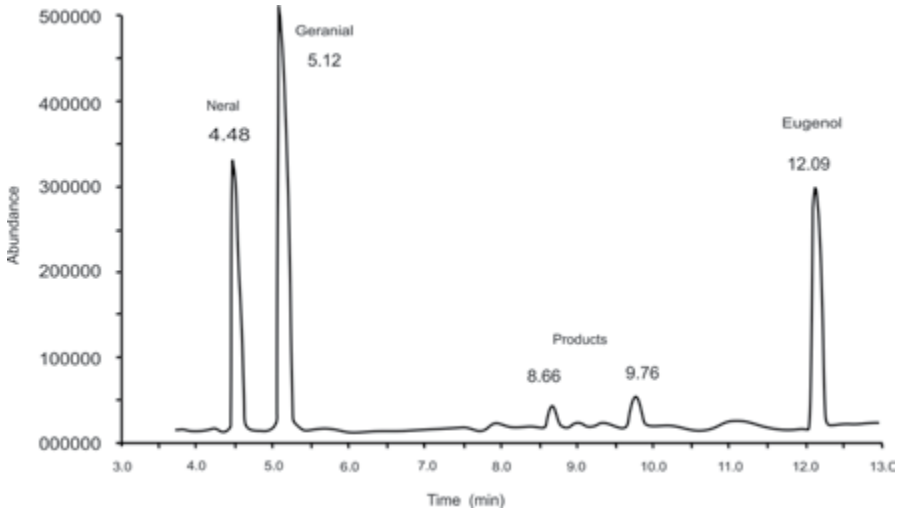


Fig. 6. Chromatogram obtained from the extract of the reaction products of the epoxidation of citral by the electrochemical process at a reaction time of 4 h.

the products generated, the percentage of loss could not be established. Fig. 7 shows the fragmentation patterns of the major products obtained by ionization through electronic impact.

As shown in the mass spectra in fig. 7a, the most intense signals were observed at m/z 82, corresponding to the base peak, and m/z 95. From the mass spectra in fig. 7b, the base peak was observed at m/z 81, and another signal was obtained at m/z 97. In both cases, the m/z signals, which were lower than the base peak, coincide with the signals observed in the mass spectra of citral isomers. By analyzing the fragments of each signal, a

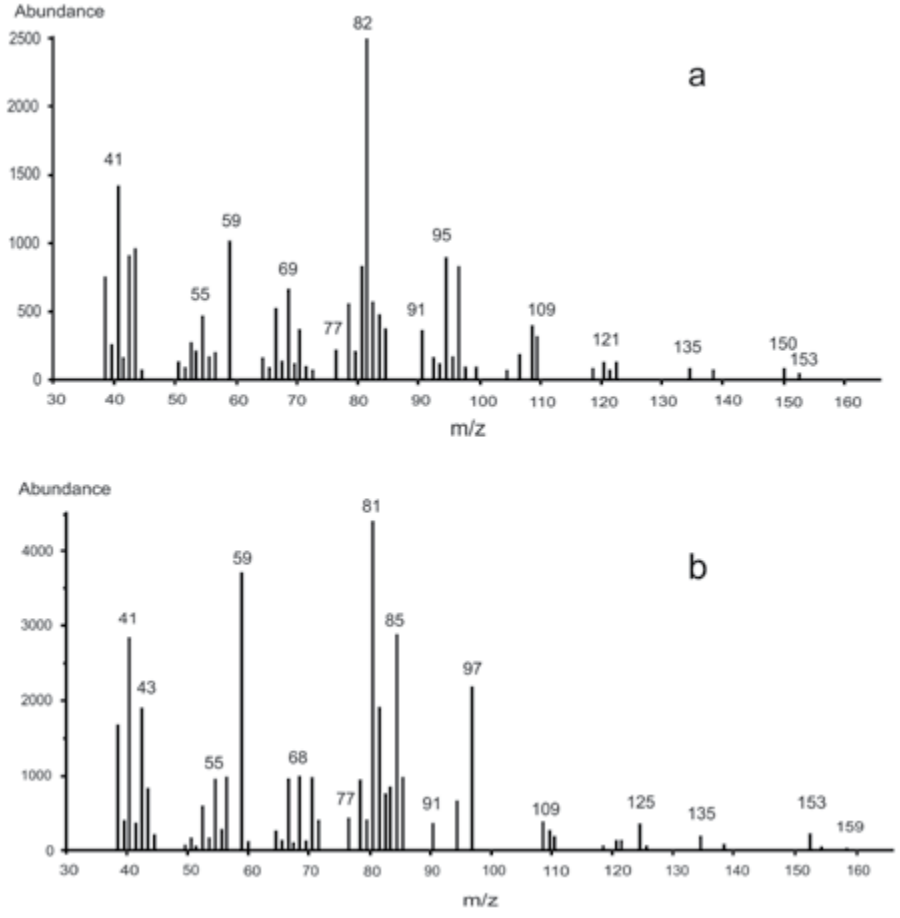


Fig. 7. Mass spectra obtained via electronic impact, showing signals at retention times of a) 8.66 min b) 9.76 min, from Fig. 5.

partition mechanism (Figures 8 and 9) was observed, where the starting species neral epoxide was generated, whose fractioning pattern coincided with the mass spectra in fig. 7a, and geranial epoxide whose fractioning pattern coincided with the mass spectra in fig. 7b.

The characteristic fragments for each citral epoxide had the formula $C_{10}H_{16}O_2$, consistent with the signal at m/z 168; this signal was not visible in the spectrum; however, despite having equal molecular mass, the neral and geranial epoxide isomers exhibited different fragmentation processes. The principal difference lies in the m/z ratio of the base peak given that fragmentation is directly related to the spatial orientation of the aldehyde group. For neral epoxide (*cis*-citral), the carbonyl group was the closest to the carbon chain; hence, fragmentation favors the formation of a stable five-membered heterocycle, corresponding to the base peak for the said epoxide (Fig. 8). Moreover, for geranial epoxide (*trans*-citral), the carbonyl group was away from the chain, which impedes the formation of the heterocycle described for neral, and consequently, fragmentation ends, generating a different base peak (Fig. 9).

The formation of the m/z 95 fragments of neral epoxide and m/z 97 fragments of geranial epoxide was explained in the same manner as the fragment base because of the proximity of the carbon chain to the carbonyl group of the aldehyde. Neral epoxide favored the formation of a six-atom heterocycle, while in geranial epoxide, the proximity of the carbonyl as well as the formation of the heterocycle were impeded; hence, a stable linear fragment is formed. Figures 8 and 9 show the mechanisms proposed for the fragmentation of both citral epoxides based on the mass spectra from figures 7 a and b.

By analyzing the fragments, the epoxidation of citral was confirmed to occur at C_6–C_7 positions. The fragment at m/z 85 was explained as a three-membered heterocyclic system: two carbon atoms and one oxygen atom; nevertheless, this last fragment was observed with high intensity in geranial epoxide, caused by the difference in the fragmentation mechanisms justified by the position of the aldehyde group with respect to the remainder of the carbon chain. From the aforementioned result, epoxidation clearly occurs primarily at the double bond between carbons C_6 and C_7 of citral given that this bond has a higher electronic density, caused by the presence of the bonded electron-donating groups. The epoxidation described is similar in its selectivity to the process performed with peroxo species; hence, it is presumed that the active species of the catalyst is a marked electrophile.

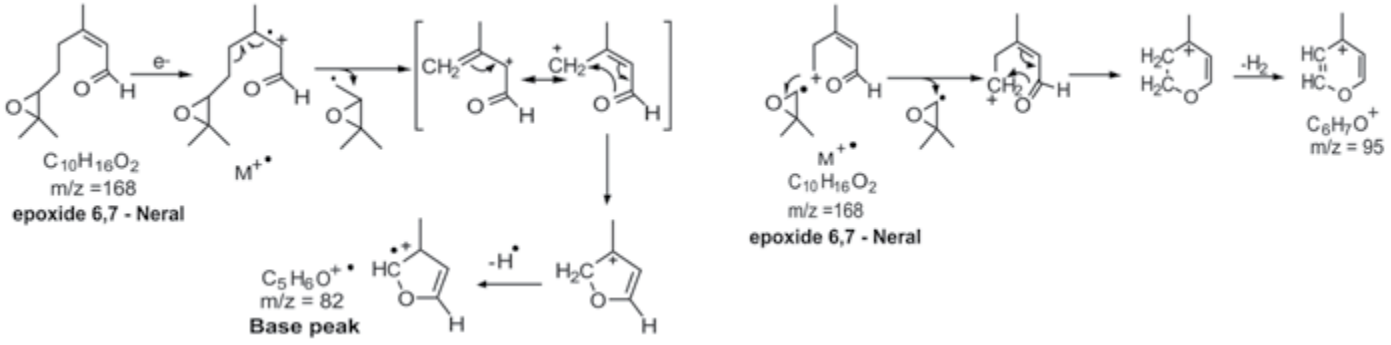


Fig. 8. Fragmentation pattern of 6, 7-neral epoxide.

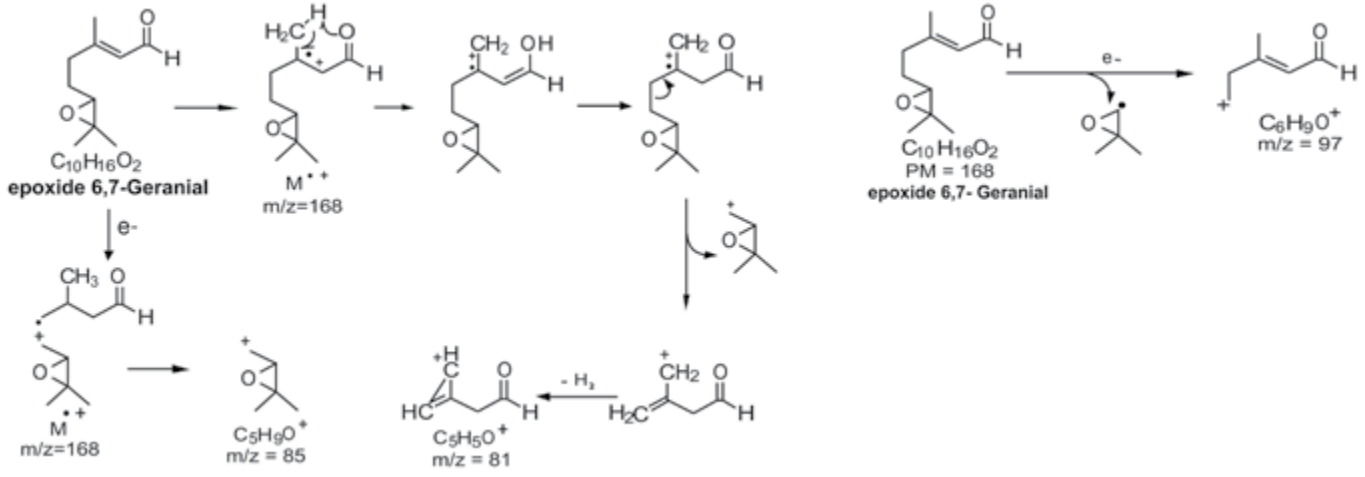


Fig. 9. Fragmentation pattern of 6, 7-geranial epoxide.

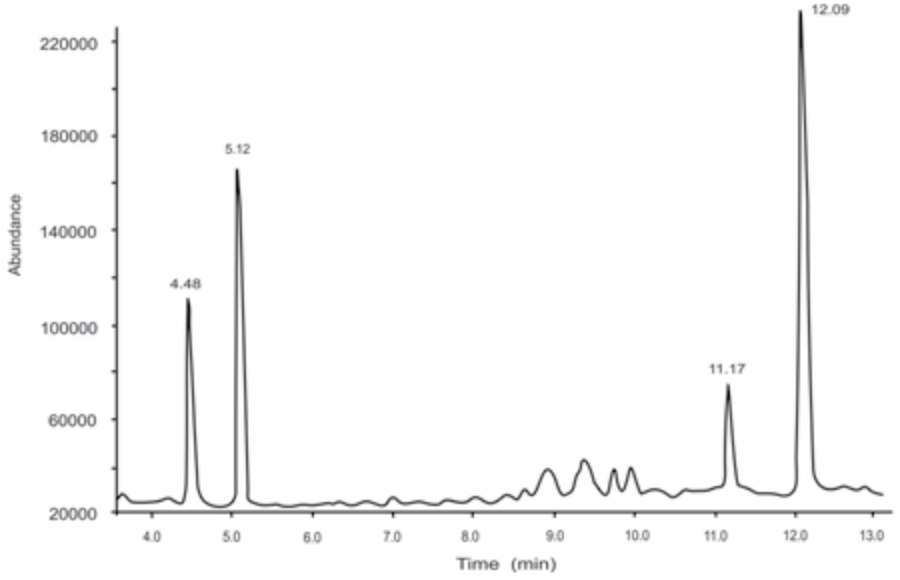


Fig. 10. Chromatogram obtained from products extracted from blank cell (system without catalyst) for chemical and electrochemical methods after 8 h of reaction.

From the gas chromatography analysis of the extract of the products from citral epoxide by the chemical method, peaks were also observed at retention times of 8.66 and 9.76; however, in this case, three additional signals with intensities and areas similar to those of epoxides were also observed, which were not identified. This is proof of the higher selectivity of the electrochemical process and suggests that ClO^- exhibits a greater affinity for the catalyst when ClO^- is added in a slow and controlled manner.

In case of the reaction blanks (systems without the presence of catalyst) in both chemical and electrochemical methods, the chromatograms obtained (Fig. 10) provided evidence for the formation of products different from the epoxides, which appeared at retention times coinciding with unidentified products of the chemical reaction; hence, it is inferred that these products correspond to the oxidation products of citral by the direct reaction with ClO^-. In addition, the major product was observed at a retention time of 11.17 min, whose fractionation pattern suggests the non-selective oxidation of double bonds of citral over simple epoxidation. This suggests that in a biphasic system, ClO^- can simultaneously participate in three reactions: first, the metallic center of the catalyst undergoes oxidation to achieve the activation of the last process, which is the complete process that culminates in the epoxidation of the substrate; second, the ligand catalyst undergoes oxidation, leading to the degradation of the complex, and finally, the direct oxidation of citral to alcohols or aldehydes.

Experimental section

Materials

HPLC-grade acetonitrile (MeCN), petroleum ether, GC-grade ethyl acetate (Fisher Scientific), citral (95%), GC–MS-grade salicylaldehyde (Aldrich Chemistry), eugenol (99%), metallic manganese (Fluka Chemika), GC-grade dichloromethane (J.T. Baker), perchloric acid (72%), hydrated potassium dibasic phosphate (99%), monohydrated potassium monobasic phosphate (99%), GC-grade hexane, platinum sheets (1 cm^2), platinum wire (0.3 mm) (99.99%), *trans*-(±)-1,2-cyclohexanediamine (99.5%), dimethylformamide (DMF), chloroform (Merck), tetrabutylammonium bromide (Aldrich), and dimethyl sulfoxide (DMSO) (Pancreac) were all used as received.

Synthesis of the H_2*t*-salcn ligand

First, salicylaldehyde was added to an aqueous solution of *trans*-(±)-1,2-cyclohexanediamine in a stoichiometric ratio of 2:1 and subjected to strong agitation for 45 min. The precipitate was filtered under vacuum, washed in water, and dried for 12 h at 70 °C.

trans-(±)-*N,N*′-bis(salicylidene)-1,2-cyclohexanediamine (H_2*t*-salcn) (**1**). Yellow powder mp: 117–119 °C, UV-Vis ($CHCl_3$, nm) 320 (π–π*); 256, (n–π*). Selected FTIR bands (KBr, cm^{-1}): 3500, ν-OH; 2930,$\nu_{(cy)}$C–H; 2855,$\nu_{(cy)}$-CH_2-; 1627, νC=N; 1499, νC=C; 1279, νC–O; 762, $\nu_{(ar)}$=C–H; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.49–1.53 (2H, mc, cyclohexane, $C_{10}H$), 1.75–1.78 (2H, mc, cyclohexane, $C_{10}H$), 1.90–1.91 (2H, mc, cyclohexane, C_9H), 1.96–2.05 (2H, mc, cyclohexane, C_9H), 3.36–3.34 (2H, m, cyclohexane, N–C_8H), 6.81 (2H, dt, aromatic, C_5H), 6.93 (2H, dd, aromatic, C_3H), 7.25 (2H, dd, aromatic,C_6H), 7.30 (2H, ddd, aromatic, C_4H), 8.29 (2H, s, -N=C_7(H)-), 13.35 (1H, s, -OH-). ^{13}C NMR (126 MHz, $CDCl_3$): δ 164.72, 160.98, 132.16, 131.49, 118.68, 118.60, 116.78, 72.69, 33.11, 24.19; EI MS *m/z*: 322 (M^+) 201 ($C_{13}H_{11}NO^+$) 122 ($C_7H_7NO^+$) 77 ($C_7H_7^+$). Elemental analysis (%): calculated: C, 74.51; H, 6.88; N, 8.69; Found: C, 74.54; H, 6.87; N, 8.58.

Electrosynthesis of the [Mn(*t*-salcn)]Cl complex

The reactions occurred at room temperature in an open system with a continuous current of 20 mA applied for 2 h in a cell comprising manganese and a platinum wire as the sacrificial anode and cathode, respectively, connected to a GW-Instek power source. The working solution was obtained by using the H_2*t*-salcn ligand (3.3 mg/mL) and lithium chloride (3.3 mg/mL) dissolved in acetonitrile with tetrabutylammonium perchlorate (0.1 M) as the supporting electrolyte. The solid formed was recovered by filtration and dried at 70 °C for 12 h.

trans-N,N′-bis(salicylidene)-1,2-cyclohexanediaminomanganese(III) chloride (**2**): Brown powder: mp > 300 °C; UV-Vis ($CHCl_3$, nm) 404 (d–d), 317 (π–π*), 254 (n–π*), 213 (n–π*). Selected FTIR bands (KBr, cm^{-1}): 3500, νH_2O; 1623, νC=N; 1314, νC–O; 753, $\nu_{(ar)}$=C–H; 515–624, νMn–O; 425, νMn–N. Elemental analysis (%): calculated: C, 58.48; H, 4.91; N, 6.82, O, 7.79; Mn, 13.37; Cl, 8.63; Found: C, 57.77; H, 4.98; N, 6.24, O, 8.78; Mn, 13.28; Cl, 8.87; $E_{1/2}$ V (SSCE) = −0.187.

Chemical epoxidation

Chemical epoxidation was conducted using a biphasic system consisting of a 15.0 mL aqueous solution of 0.20 M sodium hypochlorite and 0.05 M phosphate buffer solution (PBS) at pH 11, which were in in contact with a 0.20 M citral solution and different amounts of the [Mn(*t*-salcn)]Cl catalyst (1–15 mol%); both the citral solution and catalyst were dissolved in 10.0 mL dichloromethane.

Electrochemical epoxidation

A GW-Instek power source (0–250 V) was used with two platinum electrodes 1.0 cm^2 each and with the application of a current density of 20.0 mA/cm^2 at different times (4, 8, and 16 h) to 15.0 mL of the aqueous phase composed of 1.0 M sodium chloride in 0.05 M PBS at pH 11.0. Fine measurement of current was done by a calibrated voltammeter (Technomaster inc.) and variation of ±1.0 mA was get it mean an electronic circuit fabricated in our laboratory. Ten milliliters of the organic phase with identical composition as that used in chemical epoxidation was utilized. The system was subjected to moderate magnetic agitation throughout the process.

At the end of the reaction time, 10.0 mL of hexane was added, and the phases were separated by decantation. The aqueous phase was washed with hexane (two times with 10.0 mL each). The organic phase obtained was allowed to decant for 10 min and centrifuged for 15 min, which resulted in the separation of the catalyst insoluble in hexane. Finally, the volume of the supernatant was adjusted to 50.0 mL with hexane and was analyzed by GC–MS.

In both reaction systems (chemical and electrochemical), 100 µL aliquots were taken from the aqueous phase at 1 h intervals, 0.10 g of potassium iodide and 1.0 mL of glacial acetic acid were added to 10.0 mL of water, and the aliquot solution was back-titrated with sodium thiosulfate using starch as the indicator [35]. This back titration was used to determine the ClO^- concentration.

The products obtained from both chemical and electrochemical epoxidation were separated by column chromatography with silica (LC-Si Supelco®) with a diameter of 40 **µm as** the stationary phase and a 1:1 mixture of ethyl acetate–petroleum ether as the mobile phase, followed by GC–MS analysis. To monitor the reaction, the internal pattern method was used by the addition of 50 µL of eugenol to the crude reaction.

Conclusions

Hypochlorite exhibited a very strong oxidative capacity for the [Mn(*t*-salcn)]Cl complex, given that besides acting on the metallic center of the complex, it reacts with the ligand, resulting in the degradation of the catalyst as well as the deposition of species on the electrodes and passivation of the electrodes in the cell. Both aspects, catalyst loss and electrode passivation, decreased the yield of citral epoxide obtained from the electrochemical method as compared to that obtained from the chemical epoxidation after 4 h of reaction. Despite the aforementioned result, it may be inferred that a low concentration of ClO^- at the interface favors its reaction with the catalyst and not with the substrate, which is confirmed by the lower number of secondary products obtained by the electrochemical reaction as compared to those obtained by the chemical process.

The *trans*-(±)-*N,N′*-bis(salicylidene)-1,2-cyclohexanediaminemanganese(III) chloride complex exhibited catalytic activity directing the epoxidation of citral. However, it can migrate from the organic phase to the aqueous phase in the biphasic system. The presence of the catalyst in the aqueous phase made it more susceptible to degradation by reaction with the oxidizing agent.

The electrogeneration of the oxidizing agent in the reaction medium of a biphasic system is a viable route and a good alternative for studying and controlling chemical reactions. However, for the epoxidation of terpene, it is necessary to control the migration of the oxidized species from the catalyst toward the aqueous phase to avoid its degradation and obtain high efficiency with respect to the performance and purity of products.

Neral and geranial epoxides were confirmed as principal reaction products between citral and the [Mn(*t*-salcn)]Cl catalyst, activated by electrochemically generated ClO^-. The products were confirmed by gas chromatography–mass spectrometry. In addition, epoxidation occurred in both isomers at the double bond located between carbons at 6 and 7 positions of citral, suggesting that that double bond exhibits nucleophilicity higher than that of the double bond located between carbons 2 and 3.

The following conditions were established for the chemical epoxidation of citral: catalyst concentration of 5 mol% and reaction time of 8 h; under these conditions, the percentage of citral conversion was greater than 60%. However, by the electrochemical method, a higher reaction percentage of 42% for citral was obtained in 4 h than with the chemical method (36%).

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New Pyranoanthocyanins Synthesized from Roselle (*Hibiscus sabdariffa L.*) Anthocyanins

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Abstract. Six new pyranoanthocyanins were synthesized through the reaction between dephinidin-3-sambubioside and cyanidin-3-sambubioside, extracted from roselle calyxes, with 4-vinylphenol, acetone and 2-butanone. The reaction products were characterized by liquid chromatography coupled to mass spectrometry (HPLC-TOF-MS), ultraviolet-visible spectroscopy (UV/Vis) and high-performance liquid chromatography. Those new pigments belong to the families of pinotins and methylpyranoanthocyanins and show a hypsochromic shift, which results in a more orange colour compared to the red hue of the original anthocyanins. Therefore, these compounds could be used to obtain new colorants more stable against certain factors such as pH.
Key words: pyranoanthocyanins; roselle; 4-vinylphenol; acetone; pinotins; methylpyranoanthocyanins.

Resumen. Se sintetizaron seis nuevas piranoantocianinas a través de la reacción de la delfinidina-3-sambubiósido y cianidina-3-sambubiósido, extraídas de los cálices de flor de jamaica, con 4-vinilfenol, acetona y 2-butanona. Los productos de la reacción fueron caracterizados por cromatografía líquida acoplada a espectrometría de masas (HPLC-TOF-MS), espectroscopia ultravioleta-visible (UV/Vis) y cromatografía líquida de alta resolución (HPLC). Estos nuevos compuestos pertenecen a las familias de las pinotinas y metilpiranoantocianinas, los cuales muestran un desplazamiento hipsocrómico, lo que genera pigmentos de color más naranja en comparación con el color rojo de las antocianinas originales. Por lo que, podrían ser utilizados para obtener nuevas tonalidades para colorantes más estables ante ciertos factores como el pH.
Palabras clave: piranoantocianinas; Jamaica; 4-vinilfenol; acetona; pinotinas; metilpiranoantocianinas.

Introduction

Roselle (*Hibiscus sabdariffa* L.) is an annual shrub which belongs to family Malvaceae and grows in regions with dry tropical weather, countries like China, Egypt, Sudan, Thailand, Senegal, Tanzania and Mexico. It is known by different synonyms and vernacular names around the world and its cultivation has diverse purposes, but the most important one is to produce infusions from the calyx of their flowers [1]. Nevertheless, because of its brilliant red colour and unique flavor, its calyxes are also used to make jellies, jams, sauces, wines and beverages [2-4].

Recently there has been increasing interest in this due to their beneficial health effects and there are studies about its antihyperlipidemic, antihypertensive, antypyretic, apoptotic and antioxidant activity [5, 6]. Thus, roselle could not only be used as nutrient or colorant but also as a functional food ingredient [7]. The responsible compounds for the brilliant colour and some of mentioned activities are anthocyanins.

Anthocyanins constitute a major polyphenolic family of compounds widespread in the plant kingdom; they are of interest for the food industry as potential replacements for banned dyes [8]. However, their application has been limited because of their low stability to several factors [9-16]. Consequently, diverse research groups have been searching for new anthocyanin-based natural colorants that have better colour and stability properties [17].

In 1996, Cameira dos Santos *et al*. [18] isolated a class of anthocyanin-derived pigment. After that, Fulcrand *et al*. [19] presented a structure with an additional pyrano ring between C-4 and the hydroxyl group at C-5 of a malvidin core, demonstrating that this compound was the result of the reaction of malvidin-3-glucoside and 4-vinylphenol [20]. This pyranoanthocyanin family has been named hydroxyphenyl-pyranoanthocyanins, and their formation happens due to both hydroxycinnamic acids and 4-vinylphenols reacting with free anthocyanins. The family is also known as pinotins [21] since they were firstly isolated from Pinotage wines [22]. Later, those compounds were

discovered in other varieties of wine [23-25] and in some fruits juices [26]. Relating to the characteristics of the pinotins family, they show less polarity and a hypsochromic shift in relation to the original anthocyanins [19], plus, a higher stability against several factors such as pH [27].

On the other hand, Lu and Foo [28] observed the formation of new compounds when blackcurrant anthocyanins were extracted with aqueous acetone, proposing that this compounds were the result of the nucleophilic reaction with acetone. These derivatives named methylpyranoanthocyanins, show a yellow-orangish colour as a result of their hypsocromic effect.

Therefore, pyranoanthocyanins could be formed by the reaction of anthocyanins and small molecules [29, 30]. Their importance lies in the fact that they have shown to have a greater colour stability against pH changes and bleaching by sulfur dioxide than the original anthocyanins [31] and higher colour at similar concentration. Thus, since their discovery, pyranoanthocyanins have received much attention. Nevertheless, isolation and characterization of such pigments has proved to be difficult because of their concentration in food substrates is much lower than original anthocyanin. For this reason, they have been synthesized in model solutions for being characterized [32, 33].

The aim of the present work was to obtain new anthocyanin derived compounds which could expand the colorant range of food colorants since they exhibit different colors than starting material. For that reason, we synthesize and characterize six new pyranoanthocyanins related to the families of hydroxyphenyl-pyranoanthocyanins and methylpyranoanthocyanins. They were obtained as a result of the reaction of anthocyanins extracted from roselle (*Hibiscus sabdariffa* L.) calyxes with 4-vinylphenol, acetone and 2-butanone.

Results and discussion

Extraction of anthocyanins from roselle calyxes

Usually, roselle extracts contain four anthocyanins [34]: delphinidin-3-sambubioside (**1**), delphinidin-3-glucoside, cyanidin-3-sambubioside (**2**) and cyanidin-3-glucoside, but the majority ones are the two sambubiosides, while the concentration of glucosides is less than 7% [35]. In this study, the roselle extract which has been purified using Amberlite XAD-7, showed only two of the four common anthocyanins in roselle extracts. This mixture of delphinidin-3-sambubioside (**1**) and cyanidin-3-sambubioside (**2**) (Fig. 1) was used for the synthesis of pyranoanthocyanins. Under the HPLC conditions used, delphinidin-3-sambubioside (**1**) showed an absorption peak at 526 nm, while cyanidin-3-sambubioside (**2**), at 518 nm (Fig. 2a).

Synthesis of hydroxyphenyl-pyranoanthocyanins (3) and (4)

The formation of these products was achieved using the conditions proposed by Fulcrand *et al*. [19], which consist of reacting anthocyanin mixture with 4-vinylphenol in acid-aqueous media. Reaction was performed during 24 h, and passing that time, the presence of anthocyanins was not observed. Products were confirmed by HPLC-TOF-MS. It was observed the $[M]^+$ ion located in 713.3 m/z for (**3**) and in 697.3 m/z for (**4**), which match with the molecular weight for the proposed structure. Likewise the fragmentation pattern of anthocyanins, these pinotins showed [M-294] ion due to loss of sambubioside unit: 419.3 m/z for (**3**) and 403.2 m/z for (**4**).

The newly synthesized pyranoanthocyanins show different spectroscopic characteristics, compared with their anthocyanic counterparts. It was observed a hypsochromic shift, in which the pinotin (**3**) shows a peak of absorption at 503 nm, while pinotin (**4**) at 501 nm, therefore they present a hypsochromic shift of 23 and 17 nm, for (**3**) and (**4**), respectively (Fig. 2b). Table 1 summarizes the data for anthocyanins and pyranoanthocyanins.

Synthesis of methylpyranoanthocyanins (5) and (6)

Two members of the family of pyranoantocyanins were synthesized through the nucleophilic addition of acetone, when reacted with the methanolic mixture of anthocyanins from roselle calyxes. The reaction was monitored by HPLC during 120 h. It is worth mentioning that the ratio acetone:anthocyanin was an important factor for yield, reaching better yields with a 30:1 ratio (volume).

The resulting compounds were purified using a column Sephadex LH-20 and analyzed by HPLC and HPLC-TOF-MS. The molecular weight obtained, coincided with proposed structure and the presence of the ions $[M]^+$ and [M-294] was exhibited, demonstrating the characteristic fragmentation pattern of anthocyanins.

Methylpyranoanthocyanins show structural similarities with vitisins. It has been reported that vitisin A and B have hypsochromic shifts of 18-19 nm and 36-39 nm, respectively, depending on solvent. Bakker and Timberlake [36] proposed that hypsochromic shift was probably caused by the delocalization of the positive charge on C ring, which could be caused by resonance and for its partial residence on the oxygen atom of the newly formed D ring. They also proposed that the unusual shoulder observed in the UV spectra of vitisin is due to C-4 substitution. In the same way, the methylpyranoanthocyanins (**5**) and (**6**) have absorption peaks in 478 and 475 nm (Fig. 2c), showing a hypsochromic shift related to the original anthocyanins, but higher than that observed on vitisins (43-48 nm). Also these compounds show an unusual band in 354 and 340 nm, which is not present in anthocyanins and nor in pinotins.

Synthesis of methylpyranoanthocyanins (7) and (8)

The reaction products were certainly identified as methylpyranoanthocyanins-derived since they had similar retention times (Table 1) and UV spectrum than methylpyranoanthocyanins (**5**) and (**6**) (Fig. 2d). Furthermore, molecular weight of methylpyranoanthocyanins (**7**) and (**8**) is consistent with the insertion of

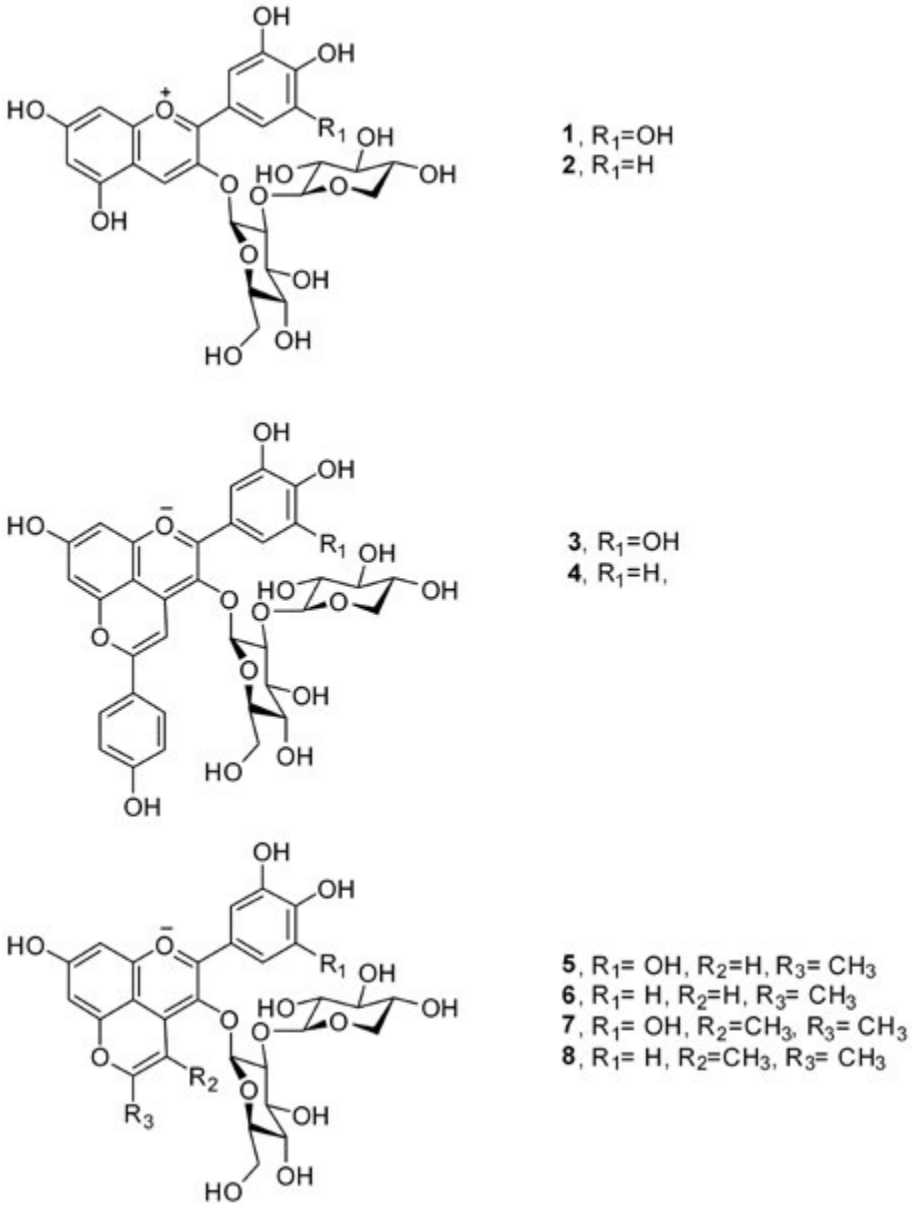

Fig. 1. Structures of the anthocyanins present in roselle (*Hibiscus sabdariffa L.*) calyxes extract and their derived pyranoanthocyanins.

2-butanone molecule. According to mechanism proposed by Lu and Foo [28], there is a dehydration (-18 units) and oxidation (-2 units) plus molecular weight of 2-butanone (+72.1 units); thus, there is a difference among molecular weight of anthocyanins **(1)** and **(2)** and methylpyranoanthocyanins **(7)** and **(8)** of 52 units. Besides, these compounds show the same characteristics of fragmentation pattern than other pyranoanthocyanins, that is, the presence of the ions $[M]^+$ and [M-294].

It is important to notice that any pyranoanthocyanin have a retention time close to anthocyanins (Table 1), indicating different polarity due to the formation of the new ring. Nevertheless, despite the retention times are close, they are longer for pyranoanthocyanins (Table 1; 3-8) respect to precedent anthocyanins (Table 1; 1 and 2). All pyranoanthocyanins synthetized in this work had a hypsochromic shift that made them more orange in comparison with the red hue of the original anthocyanins. On the other hand, the differences between delphinidin and cyanindin-derivatives of the same compound are lesser than the difference between anthocyanins; in this case, the B-ring pattern could not be a determinant factor for wavelength of maximum absorbance.

Experimental

Chemicals

Delphinidin-3-sambubioside (**1**) and cyanidin-3-sambubioside (**2**) were isolated from sun-dried roselle calyxes (*Hibiscus sabdariffa* L.) grown in Chiautla de Tapia, Puebla (980 m.a.s.l.).

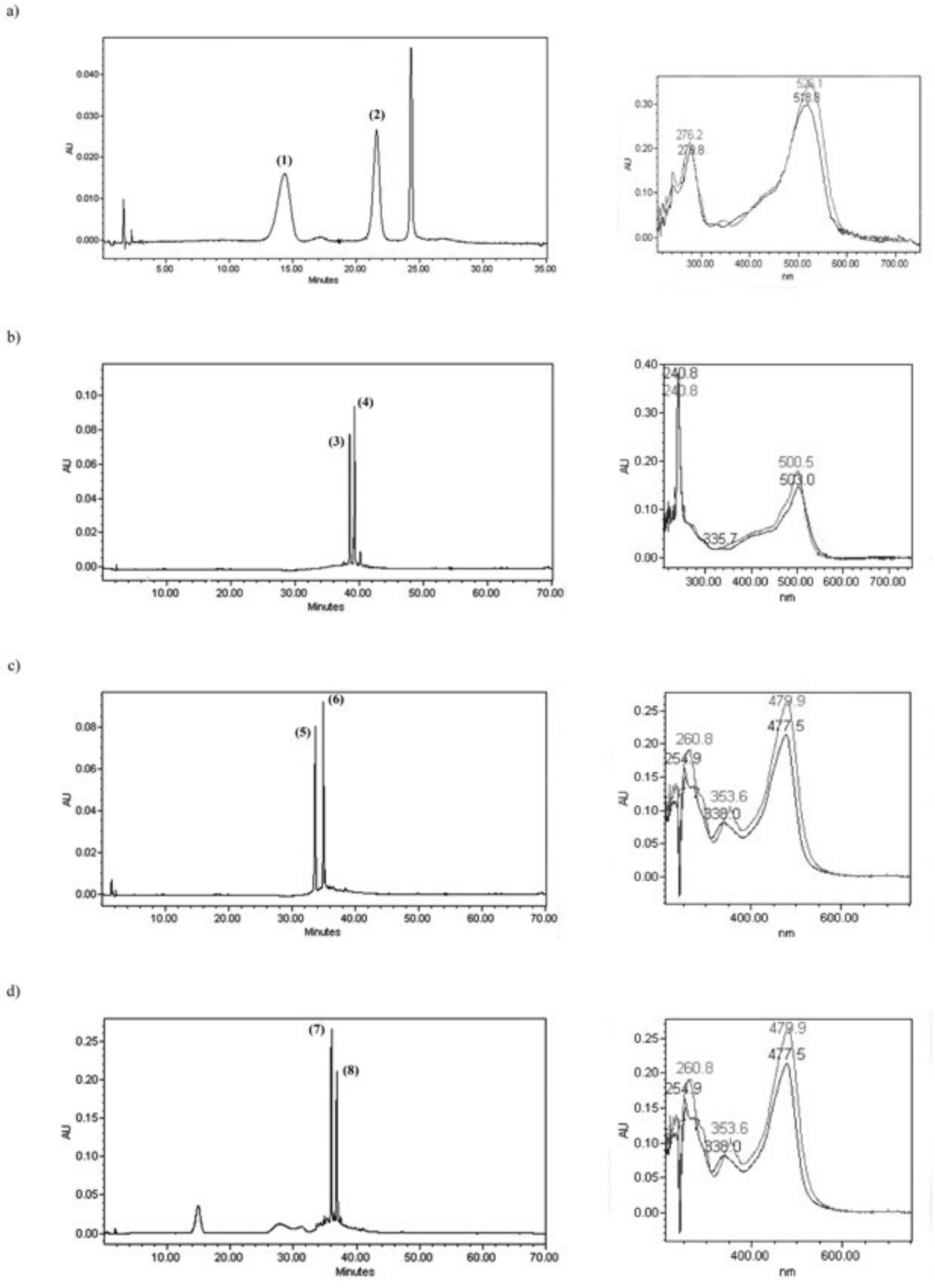

Fig. 2. HPLC chromatograms which evidence the presence of anthocyanins (520 nm) and pyranoanthocyanins (480 nm). UV-spectra for a) mixture of anthocyanins (dephinidin-3-sambubioside (1) and cyanidin-3-sambubioside (2)); b) hydroxyphenyl-pyranoanthocyanins (3) and (4); c) methylpyranoanthocyanins (5) and (6); d) methylpyranoanthocyanins (7) and (8).

Table 1. Spectroscopic and chromatographic data from roselle anthocyanins and their derivated pyranoanthocyanins.

Compound	t_R (min)	l_{max} (nm)	m/z	hypsochromic shift (nm)
Delfinidin 3-sambubioside (**1**)	12	526	$[M]^+$ 597.2; [M-294] 303.1	
Cyanidin 3-sambubioside (**2**)	18	518	$[M]^+$ 581.2; [M-294] 287.1	
Pinotin (**3**)	38.5	503	$[M]^+$ 713.3; [M-294] 419.3	23
Pinotin (**4**)	39.3	501	$[M]^+$ 697.3; [M-294] 403.2	17
Methylpyranoanthocyanin (**5**)	33.7	478, 354	$[M]^+$ 635.2; [M-294] 341.1	48
Methylpyranoanthocyanin (**6**)	34.9	475, 340	$[M]^+$ 619.2; [M-294] 325.1	43
Methylpyranoanthocyanin (**7**)	36.0	480, 353	$[M]^+$ 649.2; [M-294] 355.2	46
Methylpyranoanthocyanin (**8**)	36.9	478, 338	$[M]^+$ 633.2; [M-294] 339.1	40

Amberlite XAD-7 and Sephadex LH-20 were purchased from Sigma-Aldrich. Water and acetonitrile used in chromatography assays were HPLC-grade and purchased from Merck. Formic acid >88%, acetone reactive grade, clorhidric acid, 2-butanone and 4-vinylphenol were purchased from Sigma-Aldrich. Hexane, ethyl acetate and methanol used on columns were industrial grade double distilled.

Anthocyanin extraction

Roselle calyxes (*Hibiscus sabdariffa* L.) were previously grounded and then macerated using methanol for 2 h, using a ratio 40 g /200 mL. The extract obtained was filtrated, vacuum-dried, and adsorbed in Amberlite XAD-7 (64 g). The adsorbed resin was packed on a column (3.2 x 45 cm), then eluted with acid water (2 L, 0.01% HCl), hexane (1 L), ethyl acetate (1 L), and acid methanol (800 mL, 0.01% HCl). The water, hexane and ethyl acetate fractions were discarded; meanwhile, the methanol fraction was vacuum-distilled for obtaining a mixture composed by delphinidin-3-sambubioside (**1**) and cyanidin-3-sambubioside (**2**).

Chromatographic profile

HPLC of Anthocyanins. The mixture obtained above, was analyzed by HPLC Waters 600 equipped with 20 µL loop, using a reverse phase column C18 LiChroCART (25 x 0.4 cm, 5 µm). A gradient was established using acetonitrile (A) and 4.5% formic acid (B): isocratic 9:91 (A:B) for 25 min, 26-28 min, 100:0 (A:B) and 28-30 min, 9:91 (A:B) at a flow rate of 1.5 mL/min. Detection was carried out using a Waters 996 PDA detector at 520 nm.

*HPLC of pyranoanthocyanins***.** Products obtained were analyzed using the same column and flow rate described earlier, but the gradient was changed: isocratic 9:91 (A:B) for 20 min, 20-25 min, 5:95 (A:B); 25-65 min 100:0 (A:B), 65-70 min, 9:91 (A:B). Detection was carried out at 480 nm.

*HPLC-TOF-MS***.** Pyranoanthocyanins were analyzed by HPLC Agilent 1200 series coupled to Agilent 6220 series time-of-flight mass spectrometer (TOF-MS) system. Mass spectra were acquired using an electrospray source in positive mode (ESI+), from 200-1200 m/z. A gradient was established using acetonitrile (A) and 4.5% formic acid (B) using a C18 column with a flow rate of 0.8 min/mL in the following conditions: 9:91 (A:B) at 0 min, 0-30 min, 60:40 (A:B), 30-32 min, 0:100 (A:B), isocratic 0:100 (A:B) for 5 min, 37-39 min 9:91 (A:B).

Synthesis of hydroxyphenyl-pyranoanthocyanins (3) and (4)

A mixture (150 mg) of the extracted anthocyanins was dissolved in 40 mL of a solution of aqueous 0.001M HCl, using a flask provided with a stirrer. Then 1 mL of 4-vinylphenol was added. The mixture was stirred for 24 h. After this time, the mixture was filtrated and was adsorbed in a Sephadex LH-20 column (1 x 9 cm), then was eluted using water. The resulting fraction was lyophilized.

Synthesis of methylpyranoanthocyanins (5) and (6)

Using a flask provided with a stirrer, 200 mg of mixture of anthocyanins were dissolved in 6 mL of methanol and 14 mL of acetone. Reaction mixture was stirred for 120 h; then the solvent was vacuum-distilled and absorbed in a Sephadex LH-20 (1 x 9 cm) which was eluted using water. The resulting fraction was lyophilized.

Synthesis of methylpyranoanthocyanins (7) and (8)

Using a stirred-flask, 200 mg of mixture of anthocyanins were dissolved in 6 mL of methanol and 14 mL of 2-butanone. The reaction and purification were developed under the same conditions than those described for the synthesis of methylpyranoanthocyanins (**5**) and (**6**).

Conclusions

Nucleophilic reactions between roselle anthocyanins and 4-vinylphenol, and some ketones were achieved. These reactions

generate products with different spectral and chromatographic properties than those from original anthocyanins.

Roselle anthocyanins react with 4-vinylphenol to generate hydroxyphenyl-pyranoanthocyanins derivatives. This pyranoanthocyanin family can be synthesized faster than other pyranoanthocyanins, and they might be used as pigments in medium- and low-acid food.

On the other hand, the anthocyanin reaction with acetone produces methylpyranoanthocyanins (**5**) and (**6**), which are relatively fast synthesized. We observed that the relation anthocyanin-acetone-solvent is an important factor to obtain them, as confirmed from preliminary ratios assayed for the reaction (10:1, 20:1, 30:1, 40:1, 50:1, and 80:1, acetone:anthocyanin), and the best was selected in terms of HPLC signal intensity. These compounds had a more pronounced hypsocromical effect showing a yellow-orange colour; in this way, they expanded the colour range in their application as food colorants.

Methylpyranoanthocyanins **(7)** and **(8)** were synthesized in the same manner and they had similar spectral properties, nevertheless further investigations are necessary to determine steric hindrance on pyranoanthocyanin formation when ketone chain is increased.

Pyranoanthocyanins are no just more stable than anthocyanins but also they display more colours depending on their structure, we proposed that methodologies used here could expand the structural variety of pyranoanthocyanins.

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Essential Oil Chemical Composition of *Mentha mozaffarianii* Jamzad Seeds

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Abstract. The seeds essential oil of the endemic species *Mentha mozaffarianii* growing wild in the south of Iran was analyzed by gas chromatography (GC) and GC-mass spectrometry (GC-MS). Characterization of individual components was performed using a commercial mass spectrometry library, and 25 components were identified. This analysis showed the presence of 3 volatile components, including piperitenone (35.6%), piperitone (27.1%) and 1,8-cineol (10.7%) as the main components.
Key words: *Mentha mozaffarianii*; essential oil; piperitenone; piperitone.

Resumen. Se obtuvo una muestra del aceite esencial de semillas de la planta endémica *Mentha mozaffarianii* en el sur de Irán y se analizó por GC y GC-MS. La caracterización de los compuestos individuales se realizó utilizando una biblioteca comercial para espectrometría de masa y se identificaron 25 compuestos. Este análisis mostró la presencia de tres compuestos volátiles, piperitenone (35.6%), piperitone (27.1%), y 1,8-cineol (10.7%) como principales componentes.
Palabras clave: *Mentha mozaffarianii*; aceite esencial; piperitenone; piperitone.

Introduction

The Iranian endemic plant *Mentha mozaffarianii* Jamzad belongs to the Lamiaceae family and is known locally as "Pooneh-Koohi" [1]. Six species and several subspecies of the genus *Mentha* are found in Iran, among which just *M. mozaffarianii* is endemic. It has a limited geographical range in the south of Iran and is just found in Siyahoo, Qotb-Abad, Damtang and Sikhoran in Hormozgan Province [2]. The leaves and seeds have been commonly used in Iranian traditional medicine as antiseptic, analgesic, and to treat painful menstruation, dyspepsia, arthralgia, fever, headache, common cold, and healing wound [1-3]. Literature survey revealed reports just on the essential oil composition of the leaves and the aerial parts of *M. mozaffarianii* and there was no attempt to study the essential components of *M. mozaffarianii* seeds up to now. Regarding the significant pleasant odor of the seeds, we were prompted to investigate the essential oil composition of this part of *M. mozaffarianii* for the first time.

Results and Discussion

The hydrodistillation of *M. mozaffarianii* seeds gave pale yellow oil with pleasant odor and yield of 2.4% (v/w) based on the fresh weight. Fig. 1 shows the gas chromatogram of *M. mozaffarianii* seed essential oil.

Table 1 shows the list of compounds whose GC-MS concentration is not less than 0.1% of total peak concentration. According to Table 1, 25 components were identified in the seeds essential oil which presented about 96.8% of the total composition. The major constituents of *M. mozaffarianii* seed oil were characterized as piperitenone (35.6%), piperitone (27.1%) and 1,8-cineol (10.7%). The studied essential oil comprised one hydrocarbon (0.2%), 17 monoterpenoids (94.4%), six sesquiterpenoids (3.2%) and one phenylpropanoid (0.3%).

Piperitenone as the major component of the studied oil is a monoterpene ketone. According to Fujita et al. [4] piperitenone appears first in young leaves of *Mentha* species and then converts to pulegone or piperitone via two separate pathways in older leaves. The current results showed that most of the first appeared piperitenone was converted to piperitone. High and low amounts of piperitone (27.1%) and pulegone (4.6%) respectively in the seeds oil demonstrate a characteristic metabolic pathway in *M. moaffarianii* in which piperitenone could highly be metabolized to piperitone rather than pulegone. As literature survey there were just two reports on the essential oil composition of the leaves and aerial parts of *M. mozaffarianii* [3,5]. A comparison of the results with the literature showed that the seeds oil composition was so similar to the leaves oil

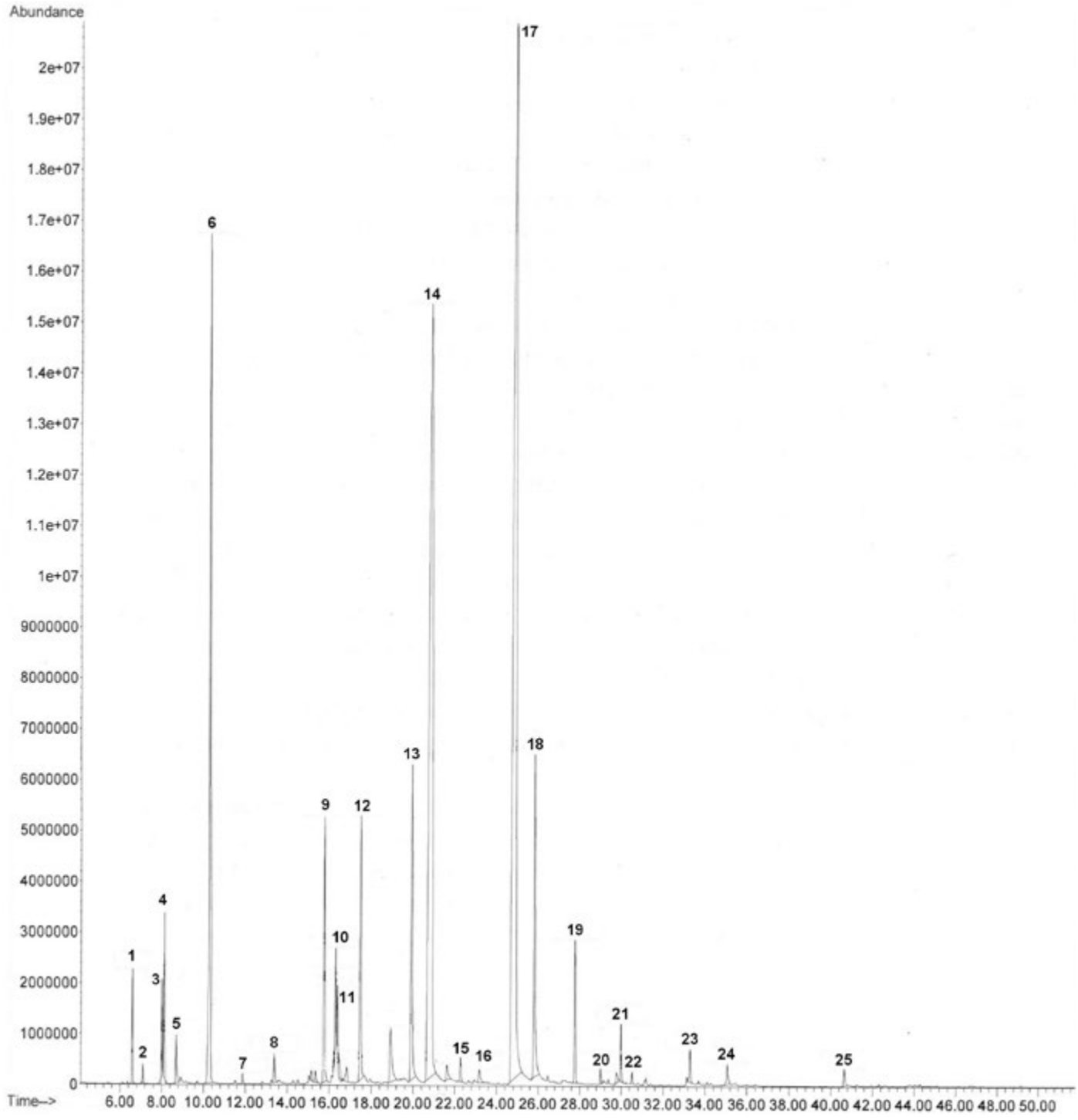

Fig. 1. Gas chromatogram of *M. mozaffarianii* seed essential oil.

composition reported by Arman et al. [3]. That is because both samples were collected from the same region in Hormozgan Province. Regarding the results reported by Arman et al [3], presence of piperitenone as the main component in the seeds and the leaves oils of *M. mozaffarianii* is characteristic. However, the piperitenone content in *M. mozaffarianii* leaves oil was reported as two times more than that in the seeds oil. Higher amounts of piperitenone (59.5%) in the essential oil of *M. mozaffarianii* leaves could be related to the stage of plant growth. According to Arman *et al*. *M. mozaffarianii* was collected at full flowering stage. Since the leaves were young at this stage, piperitenone content was expected in maximum and Arman *et al*. report also confirmed it. Mature seeds appear at the time the plant gets older. As the current results about half of

Table 1. GC-MS analysis of *M. mozaffarianii* seed essential oil.

Compound[a]	KI[b]	KI[c]	Percentage
1. α-Pinene	942	939	0.9
2. Camphene	950	954	0.2
3. Sabinene	972	975	0.7
4. β-Pinene	976	979	1.4
5. β-Myrcene	996	991	0.5
6. 1,8-Cineol	1028	1031	10.7
7. *cis*-Sabinene hydrate	1074	1070	0.1
8. Linalool	1101	1097	0.3
9. Menthone	1149	1153	3.0
10. Borneol	1166	1169	1.0
11. Terpinene-4-ol	1179	1177	0.3
12. α-Terpineol	1190	1189	3.3
13.Pulegone	1241	1237	4.6
14. Piperitone	1255	1253	27.1
15. Bornyl acetate	1287	1289	0.3
16. Thymol	1293	1290	0.3
17. Piperitenone	1339	1343	35.6
18. Piperitenone oxide	1372	1369	4.4
19. *trans*-Caryophyllene	1418	1419	1.6
20. α-Humulene	1457	1455	0.2
21. Germacrene D	1489	1485	0.6
22. Bicyclogermacrene	1496	1500	0.1
23. Caryophyllene oxide	1579	1583	0.4
25. 6,10,14-Trimethyl-2-pentadecanone	1843	1840	0.2
Total			96.8

[a] Compounds listed in order of elution.
[b] KI (Kovats index) measured relative to *n*-alkanes (C_9-C_{28}) on the non-polar DB-5 column under condition listed in the Materials and Methods section.
[c] KI, (Kovats index) from literature.

the piperitenone content has converted to piperitone. Absence of piperitenone epoxide in the seeds oil is considerable. It was reported by Arman *et al*. [3] as the second major component in the leaves oil of *M. mozaffarianii*. Rustayian *et al*. [5] reported 1,8-cineol with a high amount of 53.5% in the essential oil of aerial parts of *M. mozaffariani* while it contained 10.7% of the seed oil. Differences between *M. mozaffarianii* seeds oil chemical profile and that of the leaves reported by Rustayian *et al*. could be mainly related to the factors such as geographic origin and the season where the collection took place.

As piperitenone is found to be one of the main metabolites of the potent hepatotoxin, pulegone in the body [6], *M. mozaffarianii* could be regarded as a toxic plant and due to its traditional use as a folklore medicine future toxicology investigations are suggested.

This paper presents the essential oil composition of seeds of the endemic species *M. mozaffarianii* for the first time. Regarding the essential oil major components, further biological studies are suggested to investigate the pharmacological and therapeutic properties of the seeds.

Experimental

Plant material

Fresh seeds of *M. mozaffarianii* were collected in June 2015 from Bekhan village, Fareghan, Hadji-Abad County (Tangezaq Mountains), Hormozgan Province, Iran: (28°18′33″N, 55°54′06″E, 1700 m). Specimens were identified by R. Asadpour and voucher was deposited in the Herbarium of Pharmaceutical Sciences Branch, Islamic Azad University (IAUPS), Tehran under code number 419-PMP/A. Seeds were powdered and submitted to hydrodistillation in a Clevenger-type apparatus for 3 hours. At the end of distillation the oil was collected, dried with anhydrous Na_2SO_4, measured, and transferred to a

clean glass vial and kept at a temperature of −18 °C for further analyses.

Analysis of the essential oil

Oil sample analyses were performed on a HP-6890 gas chromatograph (GC) equipped with a FID and a DB-5 capillary column, 30 m × 0.25 mm, 0.25 μm film thickness, temperature programmed as follows: 60-240 °C at 4 °C/min. The carrier gas was N_2 at a flow of 2.0 ml/min; injector port and detector temperature were 250 °C and 300 °C, respectively. Sample was injected by splitting and the split ratio was 1:10. GC-MS analysis was performed on a Hewlett-Packard 6890 /5972 system with a DB-5 capillary column (30 m × 0.25 mm; 0.25 μm film thickness. The operating conditions were the same conditions as described above but the carrier gas was He. Mass spectra were taken at 70 eV. Scan mass range was from 40-400 *m/z* at a sampling rate of 1.0 scan/s. Quantitative data were obtained from the electronic integration of the FID peak areas. The components of the oil were identified by their retention time, retention indices, relative to C_5-C_{28} n-alkanes, computer matching with the Wiley 275.L library and as well as by comparison of their mass spectra with data already available in the literature [7,8]. The percentage of composition of the identified compounds was computed from the GC peaks areas without any correction factors and was calculated relatively. The analyses of the essential oil are the average of three replicates.

Acknowledgments

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Article

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Divergent and Selective Functionalization of 2-Formylpyrrole and its Application in the Total Synthesis of the Aglycone Alkaloid Pyrrolemarumine

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Abstract. Diverse 1,2- and 1,2,5-substituted pyrroles were efficiently prepared through a regioselective functionalization of 2-formylpyrrole (**5a**). This methodology was applied for the first total synthesis of pyrrolemarumine (**4b**), the aglycone of the corresponding natural pyrrole alkaloid 4"-*O*-α-L-rhamnopyranoside. The synthesis of **4b** was achieved starting from **5a** through a seven-step process in 28% overall yield.
Key words: 2-formylpyrrole; Vilsmeier-Haack formylation; pyrrole alkaloids; pyrrolemarumine.

Resumen. Se prepararon eficientemente diversos pirroles 1,2- y 1,2,5-subtituidos a través de la funcionalización regioselectiva del 2-formilpirrol (**5a**). Esta metodología se aplicó en el desarrollo de la primera síntesis total de la pirrolemarumina (**4b**), que es la aglicona del alcaloide pirrólico natural correspondiente 4"-*O*-α-L-ramnopiranósido, la cual se realizó partiendo de **5a** a través de un proceso en siete etapas y en un rendimiento global de 28%.
Palabras clave: 2-formilpirrol; formilación de Vilsmeier-Haack; alcaloides pirrólicos; pirrolemarumina.

Introduction

Pyrroles are ubiquitous five-membered heterocycles forming part of the structure of a large number of natural products [1] and pharmacologically active compounds [2]. Alkaloids isolated from diverse natural sources, such as higher order plants [3] and marine species [4] display a substituted single pyrrolic ring or pyrrole-fused polycyclic or heterocyclic scaffolds, which are distinguished by their strong antibiotic, anticancer, antifeedant and antiviral activity.

Pyrrole-2-aldehyde derivatives represent a unique variety of alkaloid natural products isolated from fungi, microorganisms, plants, and edible fruits, among other natural sources. For example, jiangrines A-E (**1a-e**) and pyrrolezanthine (**1f**), which exhibit anti-inflammatory activity, were isolated from the fermentation broth of *Jiangella gansuensis* (Fig. 1) [5]. Fusarine (**1g**) is a naturally occurring 2-acyl pyrrole isolated from the culture broth of *Fusarium incarnatum* (HKI0504), an endophytic fungus of the mangrove plant *Aegiceras corniculatum* [6]. Makomotines **2a-c** were isolated from an edible gall called Makomotake (*Zizania latifolia* infected with *Ustilago esculenta*) found in Japan, China and other Asian countries [7]. Pyrrole alkaloids **2d-g** have been isolated from an extract of the fruits of *Lycium chinense* Miller (Solanaceae), which is used as a traditional tonic medicine for treating liver and kidney failures [8]. From the seeds of watermelon (*Citrullus lanatus* (*Thunb.*)), 2-formyl pyrroles **3a-b** were isolated that exhibit modest inhibitory activity on melanogenesis [9]. The naturally occurring pyrrole alkaloid pyrrolemarumine 4"-*O*-α-L-rhamnopyranoside (**4a**), recently isolated from leaves of *Moringa oleifera* Lam., was hydrolyzed to yield the new aglycone pyrrolemarumine (**4b**) [10] (Fig. 2). Despite their potential biomedical properties and relatively simple structure, the synthesis for most of these unusual 1,2- and 1,2,5-substituted pyrrole alkaloids has not yet been reported [11]. Therefore, a synthetic approach to any of these compounds needs to be designed on the basis of the selective functionalization of pyrrole or 2-formylpyrrole (**5a**).

The structure and promising pharmacological profile of these compounds fits well into our ongoing research program of carrying out the transformation of simple five-membered heterocycles into fine chemicals and more complex natural products [12]. Hence, we herein investigated the reactivity of 2-formylpyrrole (**5a**) as the key starting material for the synthesis of a series of 1,2- and 1,2,5-trisubstituted pyrroles, as well as in the first total synthesis of compound **4b**.

Results and discussion

Synthesis of 1,2-Disubstituted Pyrroles

2-Formylpyrrole (**5a**) was used as the starting material for the divergent synthesis [13] of novel 1,2-substituted pyrrole

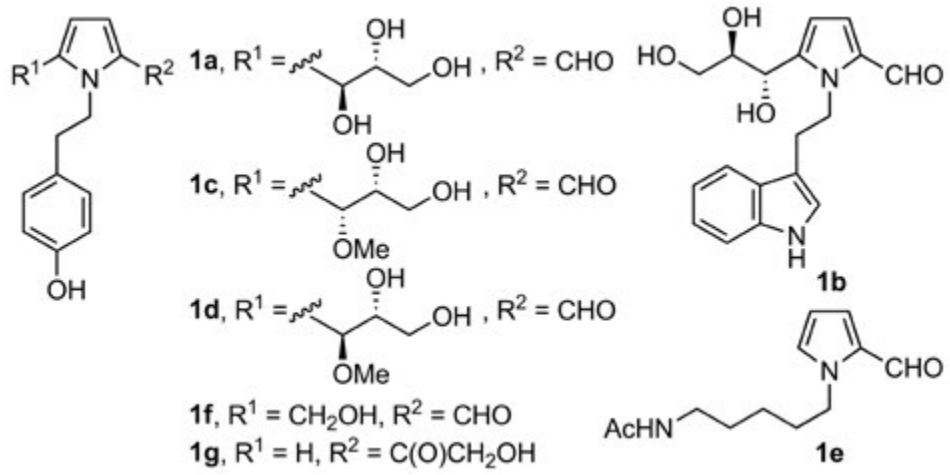


Fig. 1. Structures of jiangrines A-E (**1a-e**), pyrrolezanthine (**1f**) and fusarine (**1g**).

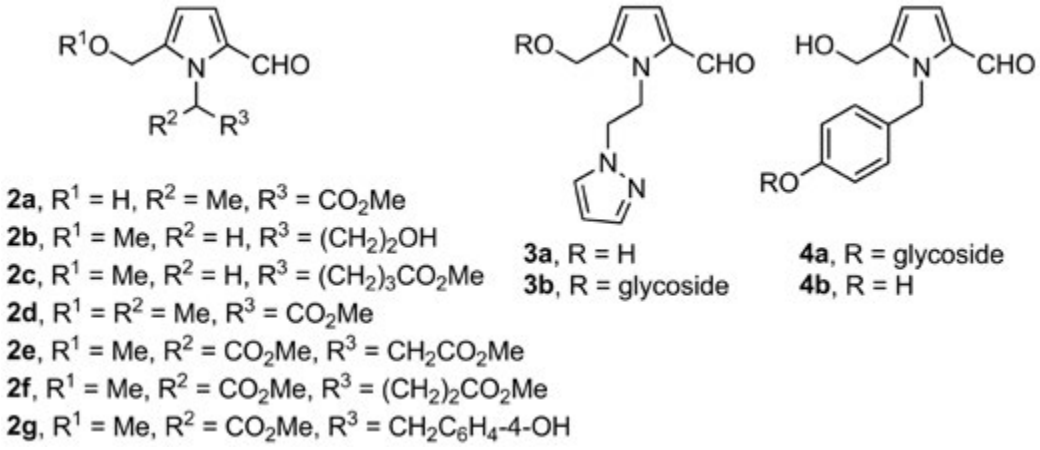


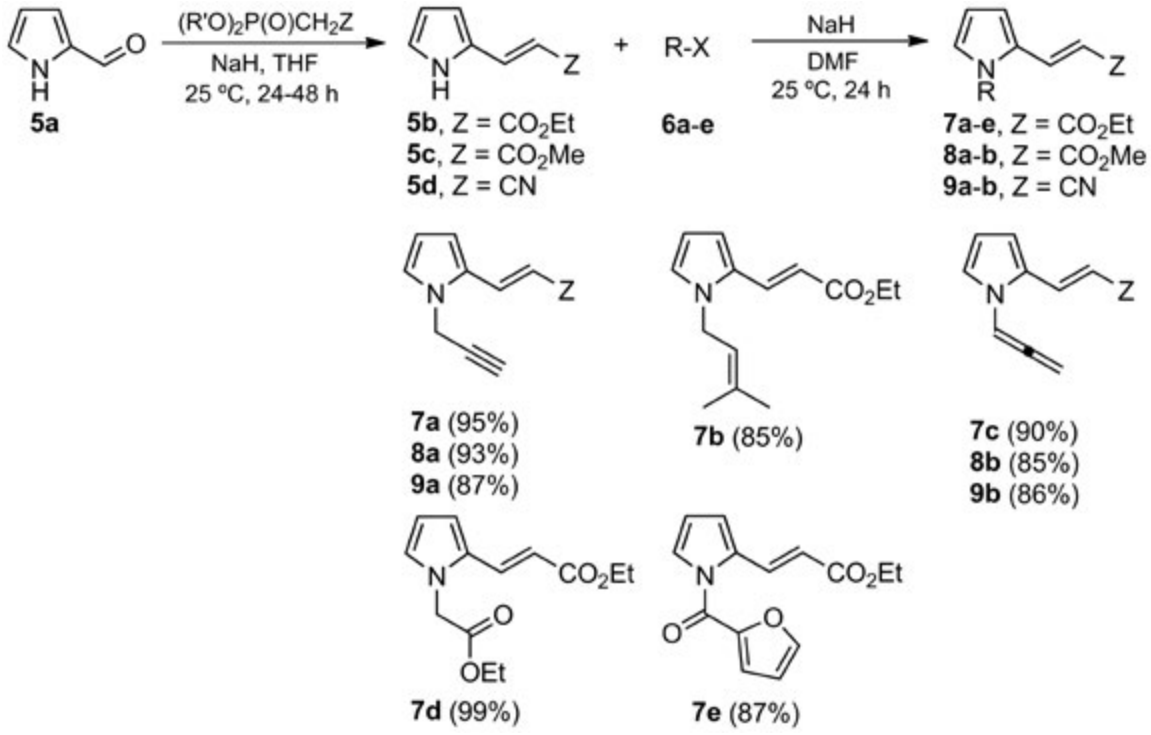
Fig. 2. Structures of makomotines **2a-c**, 2-formyl pyrroles **2d-g** and **3a-b**, pyrrolemarumine 4”-*O*-a-L-rhamnopyranoside (**4a**) and pyrrolemarumine (**4b**).

derivatives of the ethyl 3-acrylates **7a-e**, methyl acrylates **8a-b** and acrylonitriles **9a-b** (Scheme 1). These vinylogous electron-deficient pyrroles were selected because they may be applied as potential precursors for the preparation of more complex and polysubstituted pyrroles as HMG-CoA reductase inhibitors [14], whose pharmacological activity is also found in our potent hypolipidemic compounds [15].

Previous studies have reported the direct *N*-alkylation by NaH-promoted deprotonation of commercially available **5a** with diverse primary alkyl halides to furnish the series of 1-substituted 2-formylpyrroles [16]. This method was also useful for the preparation of the series of new 1,2-substituted pyrroles **7-9** starting from **5b-d**, which are the Horner-Wadsworth-Emmons derivatives of **5a**. Thus, under mild reaction conditions, pyrroles **7a-e** were synthesized in high yields (Scheme 1). Pyrrole **7c** was prepared in a single-step procedure by using **5b**, propargyl bromide (**6a**) and an excess of NaH. Similarly, in the case of methyl acrylate **5c**, the reaction with **6a** provided either *N*-propargyl pyrrole **8a** or *N*-allenyl pyrrole **8b** in high yields. The latter was generated by direct isomerization of **8a** or through the cascade alkylation of **5c** with **6a** in the presence of an excess of NaH, similar to **7c**. Likewise, *N*-alkylation of 3-(pyrrol-2-yl)acrylonitrile (**5d**) led to *N*-substituted pyrroles **9a-b** in good yields, under similar mild reaction conditions.

Regioselective Synthesis of 1,2,5-Substituted Pyrroles

Evaluation of the reactivity and regioselectivity of the formylation of pyrroles **7** was exemplified by using pyrroles **7a-c**. Thus, the latter were formylated under the usual Vilsmeier-Haack conditions to give rise to the corresponding 5-formyl derivatives **10a-c** in good yields (81-88%) (Scheme 2). Interestingly, in all the substrates the C-5 formyl regioisomer was exclusively obtained and no mixtures of the three possible C-3/C-4/C-5 formyl isomers were observed. This is in agreement with previous reports for an analogous substrate [17], though there is a broad tendency to provide no selective ratios of regioisomers [17,18].



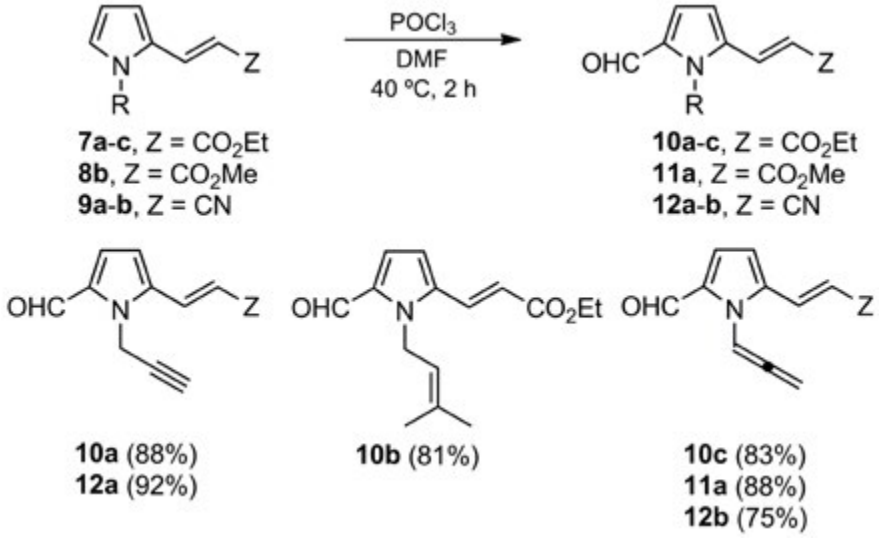
Scheme 1. Preparation of 1,2-disubtituted pyrroles **7a-e**, **8a-b**, and **9a-b**.

A behavior similar to pyrroles **7a-c** was found when methyl acrylate **8b** and acrylonitriles **9a-b** were formylated to afford the corresponding 1,2,5-trisubstituted pyrroles **11a** and **12a-b**, respectively.

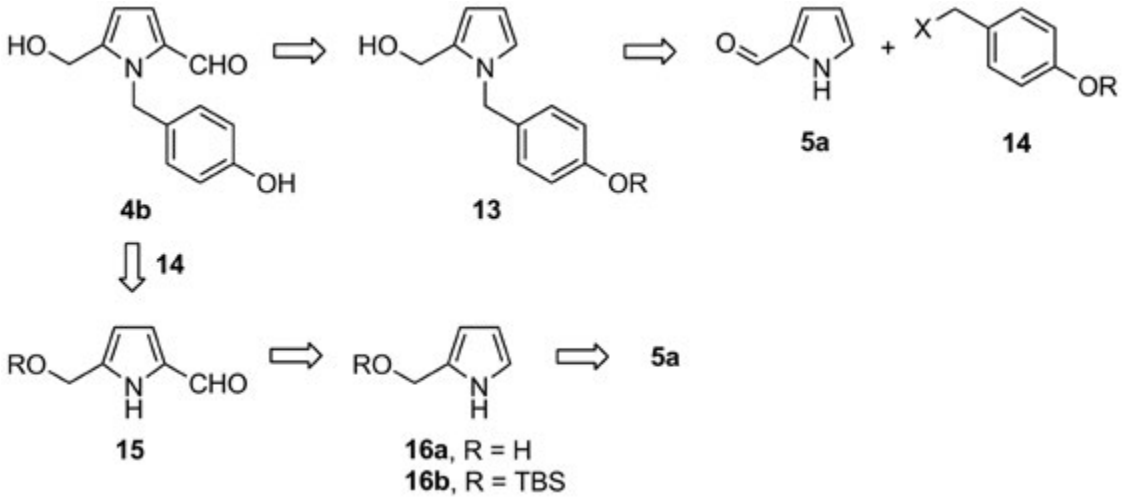
The highly regioselective preparation of these 1,2,5-trisubstituted pyrroles in good overall yields prompted us to explore the use of 2-formylpyrrole (**5a**) as an efficient starting material for the total synthesis of a naturally occurring 2-formyl pyrrole alkaloid, such as pyrrolemarumine (**4b**). The latter compound was chosen because most of the natural alkaloids illustrated in figures 1-2 display the same 2,5-functionalities in the pyrrole core.

Total Synthesis of Pyrrolemarumine (4b)

The total synthesis of pyrrolemarumine (**4b**), the aglycone of the natural pyrrole alkaloid **4a**, was designed based on the insights gained from observing the behavior of 2-formylpyrrole



Scheme 2. Synthesis of formyl pyrroles **10a-c**, **11a** and **12a-b**.

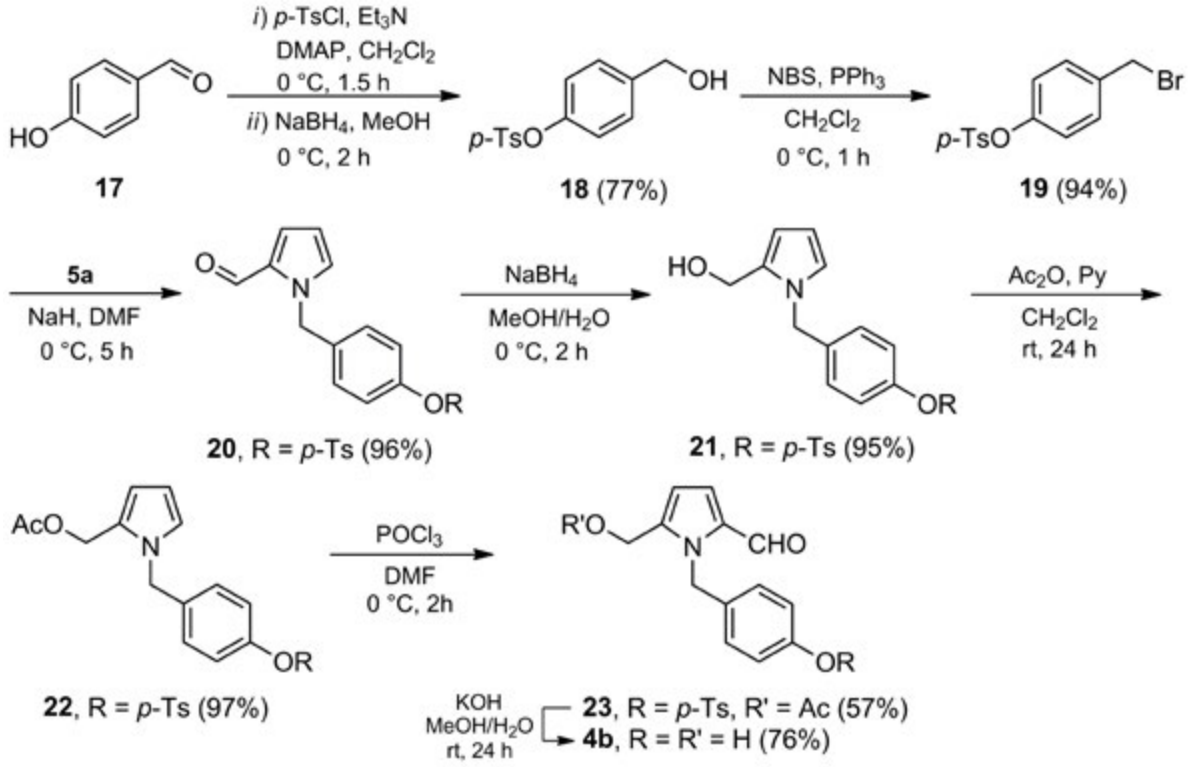


Scheme 3. Dual retrosynthesis for the preparation of the aglycone pyrrolemarumine (**4b**).

(**5a**) with the diverse reagents herein described. A dual retrosynthetic scheme was proposed (Scheme 3), which included the approach starting from the *N*-benzylation of **5a**, followed by formylation of intermediate **13** to furnish the desired product **4b**. The alternative more convergent pathway would be the *N*-benzylation of 2,5-disubstituted pyrrole **15**, which would be previously functionalized from **5a**.

Because of the obvious advantages of a convergent synthesis, the second approach was investigated first. Although pyrrole **5a** was readily reduced with sodium hydride to yield the corresponding 2-hydroxymethyl pyrrole (**16a**), this had to be protected with a TBS group to afford the silane derivative **16b** and in this way avoid decomposition. However, further degradation of this substrate under the formylation conditions led us to abandon this route and attempt the first approach.

In order to introduce the benzyl moiety into the pyrrole framework, the synthetic route followed the reaction conditions depicted in Scheme 1, whereby the benzyl bromide derivative



Scheme 4. Total synthesis of the aglycone pyrrolemarumine (**4b**).

19 gave 2-formylpyrrole **20** in high yield (Scheme 4). Derivative **19** was prepared from 4-hydroxybenzaldehyde (**17**) in good overall yield (72%) through a two-step reaction sequence, including intermediate **18**.

The reduction of **20** with sodium borohydride provided the corresponding alcohol **21** in high yield, followed by acetylation to yield acetate **22**. This protection was provided due to the instability shown by the hydroxyl group during the subsequent formylation step, which is similar to what occurred during the first approach. The latter reaction carried out under standard conditions brought the formyl group into the desired position of the pyrrole ring, resulting in **23** in a modest yield. Hydrolysis of the protective groups of the latter compound furnished the desired product **4b** in a 43% overall yield for the two steps, and in a 28% overall yield for the seven steps starting from **17**. The spectral data of the synthetic product **4b** was in agreement with the data reported for the aglycone natural product [10].

Conclusions

In summary, a divergent synthetic approach for the preparation of 1,2-di- and 1,2,5-tri-substituted pyrroles starting from 2-formylpyrrole (**5a**) has been achieved, including the first total synthesis of the aglycone alkaloid pyrrolemarumine (**4b**) in a high overall yield. The scope and efficiency of this approach is currently under evaluation for the synthesis of other 1,2,5-tri-substituted pyrrole alkaloids from the series of natural compounds **1**-**3**, and the results will be reported in due course.

Experimental Section

General: Melting points were determined with an Electrothermal capillary melting point apparatus. IR spectra were recorded on a Perkin-Elmer 2000 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury (300 MHz) and Varian VNMR (500 MHz) instruments, with $CDCl_3$ as the solvent and TMS as internal standard. Signal assignments were based on 2D NMR spectra (HMQC, HMBC). Mass spectra (MS) were recorded on Polaris Q-Trace GC Ultra (Finnigan Co.) and Hewlett-Packard 5971A spectrometers. High-resolution mass spectra (HRMS), in electron impact mode, were obtained with a Jeol JSM-GCMateII apparatus. Elemental analyses were performed on a CE-440 Exeter Analytical instrument. Analytical thin-layer chromatography was carried out using E. Merck silica gel 60 F_{254} coated 0.25 plates, visualized by using a long- and short-wavelength UV lamp. Flash column chromatography was performed over Natland International Co. silica gel (230-400 and 230-400 mesh). All air moisture sensitive reactions were carried out under N_2 using oven-dried glassware. THF was freshly distilled over sodium, as was DMF and CH_2Cl_2 over CaH_2, prior to use. MeOH was distilled over sodium. Et_3N was freshly distilled from NaOH. All other reagents were used without further purification.

Ethyl (*E*)-3-(1*H*-Pyrrol-2-yl)acrylate (5b) [19]**:** To a solution of **5a** (0.100 g, 1.05 mmol) in anhydrous THF (2 mL) at 0 °C, NaH (60%) (0.042 g, 1.05 mmol) was added. The mixture was stirred at 0 ºC under nitrogen for 30 min and triethyl phosphonoacetate (0.235 g, 1.05 mmol) was added dropwise. After stirring at room temperature for 48 h, EtOAc (30 mL) was added, the mixture washed with water (2 x 15 mL), the organic layer dried (Na_2SO_4) and the solvent removed under vacuum. The residue was purified by column chromatography over silica gel (30 g/g crude, hexane/EtOAc, 98:2) to give **5b** (0.157 g, 90%) as a reddish solid. R_f = 0.55 (hexane/EtOAc, 7:3); mp 58-59 °C. IR (film): $\overline{\nu}$ = 2981, 1683, 1622, 1544, 1446, 1366, 1268, 1181, 973, 736 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 4.24 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 6.09 (d, *J* = 15.9 Hz, 1H, H-2), 6.25-6.29 (m, 1H, H-4'), 6.53-6.58 (m, 1H, H-3'), 6.89-6.94 (m, 1H, H-5'), 7.59 (d, *J* = 15.9 Hz, 1H, H-3), 9.34 (br s, 1H, NH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 14.3 ($CO_2CH_2CH_3$), 60.3 ($CO_2CH_2CH_3$), 110.7 (C-4'), 111.0 (C-2), 114.2 (C-3'), 122.6 (C-5'), 128.4 (C-2'), 134.6 (C-3), 168.1 (CO_2Et). MS (70 eV): *m/z* = 165 (12) $[M]^+$, 164 (22) $[M - 1]^+$, 150 (5), 138 (42), 88 (100), 86 (18), 56 (12).

Methyl (*E*)-3-(1*H*-Pyrrol-2-yl)acrylate (5c) [20]**:** Following the method of preparation for **5b**, by using **5a** (0.500 g, 5.26 mmol), NaH (60%) (0.252 g, 6.31 mmol), and trimethyl phosphonoacetate (1.140 g, 6.31 mmol) in dry THF (5 mL) and stirring at 25 ºC for 24 h, **5c** (0.782 g, 98%) was obtained as a colorless solid. R_f = 0.63 (hexane/EtOAc, 7:3); mp 78-79 °C. IR (KBr): $\overline{\nu}$ = 3261, 2947, 1683. 1628, 1552, 1328, 1414, 1303, 1231, 1193, 1132, 1030, 966, 844, 755, 738 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.75 (s, 3H, CO_2CH_3), 6.12 (d, *J* = 15.9 Hz, 1H, H-2), 6.22-6.27 (m, 1H, H-4'), 6.52-6.56 (m, 1H, H-3'), 6.88-6.92 (m, 1H, H-5'), 7.59 (d, *J* = 15.9 Hz, 1H, H-3), 9.70 (br s, 1H, NH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 51.4 (CO_2CH_3), 110.2 (C-2), 110.6 (C-4'), 114.5 (C-3'), 122.7 (C-5'), 128.3 (C-2'), 134.9 (C-3), 168.6 (CO_2CH_3). MS (70 eV): *m/z* 151 (100) $[M]^+$, 120 (42), 119 (90), 92 (36), 91 (33), 65 (25).

(*E*)-3-(1*H*-Pyrrol-2-yl)acrylonitrile (5d) and (*Z*)-3-(1*H*-Pyrrol-2-yl)acrylonitrile (5d') [21]**:** Following the method of preparation for **5b**, by using **5a** (0.500 g, 5.26 mmol), NaH (60%) (0.252 g, 6.31 mmol), diethylcyanomethylphosphonate (1.117 g, 6.31 mmol) in dry THF (5 mL) and stirring at 25 ºC for 24 h, **5d** (0.563 g, 91%) and **5d'** (0.029 g, 5%) were obtained as colorless liquids.

Data for **5d**: R_f = 0.56 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$ = 3313, 2924, 2209, 1613, 1445, 1411, 1314, 1128, 1096, 1036, 956, 796, 738 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.44 (d, *J* = 16.5 Hz, 1H, H-2), 6.22-6.30 (m, 1H, H-4'), 6.50-6.56 (m, 1H, H-3'), 6.91-6.97 (m, 1H, H-5'), 7.20 (d, *J* = 16.5 Hz, 1H, H-3), 9.46 (br s, 1H, NH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 87.0 (C-2), 110.9 (C-4'), 114.9 (C-3'), 119.9 (C-1), 123.7 (C-5'), 127.7 (C-2'), 140.0 (C-3). MS (70 eV): *m/z* 118 (100) $[M]^+$, 117 (12), 92 (11), 91 (34), 67 (13).

Data for **5d'**: R_f = 0.61 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$ = 3383, 2924, 2205, 1606, 1447, 1375, 1127, 1094, 1038, 741 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.96 (d, *J* = 11.7 Hz, 1H, H-2), 6.26-6.32 (m, 1H, H-4'), 6.57-6.64 (m, 1H, H-3'), 6.95 (d, *J* = 11.7 Hz, 1H, H-3), 6.98.-7.04 (m, 1H, H-5'), 9.63 (br s, 1H, NH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 84.4 (C-2), 110.3 (C-4'), 118.0 (C-3'), 120.0 (C-1), 123.7 (C-5'), 127.9 (C-2'), 138.0 (C-3). MS (70 eV): *m/z* 118 (32) $[M]^+$, 111 (88), 109 (56), 97 (84), 95 (93), 85 (49), 83 (59), 81 (100), 71 (58), 69 (69).

Ethyl (*E*)-3-(1-(Prop-2-yn-1-yl)-1*H*-pyrrol-2-yl)acrylate (7a): To a solution of **5b** (0.200 g, 1.21 mmol) in dry DMF (2.0 mL) at 0 ºC and under N_2**,** NaH (60%) (0.058 g, 1.46 mmol) was added. The mixture was stirred at 0 ºC for 15 min, and propargyl bromide (**6a**) (0.144 g, 1.21 mmol) was added dropwise. After stirring at 0 ºC for 1 h, EtOAc (20 mL) was added and the mixture was washed with water (2 x 10 mL). The organic layer was dried (Na_2SO_4) and the solvent removed under vacuum. The residue was purified by column chromatography over silica gel (30 g/g crude, hexane/EtOAc, 9:1) to give **7a** (0.234 g, 95%) was obtained as a pale yellow oil. R_f = 0.26 (hexane/EtOAc, 9:1). IR (film): $\overline{\nu}$ = 3288, 1696, 1622, 1468, 1365, 1279, 1265, 1174, 1034, 965, 723 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.32 (t, *J* = 7.5 Hz, 3H, $CO_2CH_2CH_3$), 2.46 (t, *J* = 2.5 Hz, 1H, H-3''), 4.24 (q, *J* = 7.5 Hz, 2H, $CO_2CH_2CH_3$), 4.76 (d, *J* = 2.5 Hz, 2H, H-1''), 6.18 (d, *J* = 15.5 Hz, 1H, H-2), 6.22 (ddd, *J* = 4.0, 3.0, 1.0 Hz, 1H, H-4'), 6.68 (dd, *J* = 4.0, 1.5 Hz, 1H, H-3'), 6.94 (dd, *J* = 3.0, 1.5 Hz, 1H, H-5'), 7.63 (d, *J* = 15.5 Hz, 1H, H-3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.4 ($CO_2CH_2CH_3$), 36.7 (C-1''), 60.2 ($CO_2CH_2CH_3$), 74.4 (C-3''), 77.3 (C-2''), 110.0 (C-4'), 112.5 (C-3'), 113.7 (C-2), 125.5 (C-5'), 128.8 (C-2'), 131.6 (C-3), 167.6 (CO_2Et). MS (70 eV): *m/z* 203 (8) $[M]^+$, 174 (16), 158 (26), 131 (34), 130 (100), 119 (16), 103 (19), 91 (24), 77 (42), 63 (24). HRMS (EI): *m/z* calcd. for $C_{12}H_{13}NO_2$ $[M]^+$: 203.0946; found 203.0936.

Ethyl (*E*)-3-(1-(3-Methylbut-2-en-1-yl)-1*H*-pyrrol-2-yl)acrylate (7b): Following the method of preparation for **7a**, by using **5b** (0.100 g, 0.61 mmol), NaH (60%) (0.029 g, 0.73 mmol) and prenyl bromide (**6b**) (0.108 g, 0.73 mmol) in dry DMF (1.0 mL), and after stirring at 0 ºC for 1 h, **7b** (0.121 g, 85%) was obtained as a reddish oil. R_f = 0.36 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$ = 2977, 1700, 1622, 1472, 1444, 1324, 1276, 1163, 1037, 968, 723 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.0 Hz, 3H, $CO_2CH_2CH_3$), 1.75 (d, *J* = 1.0 Hz, 3H, H-4'' or H-5''), 1.79 (br s, 3H, H-5'' or H-4''), 4.23 (q, *J* = 7.0 Hz, 2H, $CO_2CH_2CH_3$), 4.57 (d, *J* = 7.0 Hz, 2H, H-1''), 5.28 (tm, *J* = 6.8 Hz, 1H, H-2''), 6.13 (d, *J* = 16.0 Hz, 1H, H-2), 6.16-6.17 (ddd, *J* = 3.5, 2.5, 0.5 Hz, 1H, H-4'), 6.64 (dd, *J* = 3.5, 1.5 Hz, 1H, H-3'), 6.79 (dd, *J* = 2.5, 1.5 Hz, 1H, H-5'), 7.60 (d, *J* = 16.0 Hz, 1H, H-3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.4 ($CO_2CH_2CH_3$), 17.9 (C-4'' or C-5''), 25.6 (C-5'' or C-4''), 45.2 (C-1''), 60.1 ($CO_2CH_2CH_3$), 109.3 (C-4'), 111.5 (C-3'), 112.7 (C-2), 120.0 (C-2''), 125.3 (C-5'), 128.7 (C-2'), 132.4 (C-3), 136.5 (C-3''), 167.8 (CO_2Et). MS (70 eV): *m/z* 233 (12) $[M]^+$, 208 (25), 194 (70), 184 (57), 168 (71), 154 (100), 144 (61), 130 (82), 117 (91), 115 (65), 91 (44), 77 (26). HRMS (EI): *m/z* calcd. for $C_{14}H_{19}NO_2$ $[M]^+$: 233.1416; found 233.1413.

Ethyl (*E*)-3-(1-(Propa-1,2-dien-1-yl)-1*H*-pyrrol-2-yl)acrylate (7c): Following the method of preparation for **7a**, by using **5b** (0.100 g, 0.61 mmol), NaH (60%) (0.048 g, 1.21 mmol) and propargyl bromide (**6a**) (0.144 g, 1.21 mmol) in dry DMF (1.0 mL), and after stirring at 0 ºC for 1 h, **7c** (0.111 g, 90%) was obtained as a colorless oil. R_f = 0.23 (hexane/EtOAc, 9:1). IR (film): $\overline{\nu}$ = 2925, 1702, 1623, 1463, 1258, 1175, 1037, 852, 722 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 4.24 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 5.53 (d, *J* = 6.5 Hz, 2H, H-3''), 6.19 (d, *J* = 15.5 Hz, 1H, H-2), 6.27 (dd, *J* = 3.9, 2.7 Hz, 1H, H-4'), 6.69 (dd, *J* = 3.9, 1.5 Hz, 1H, H-3'), 6.94 (dd, *J* = 2.7, 1.5 Hz, 1H, H-5'), 7.04 (t, *J* = 6.5 Hz, 1H, H-1''), 7.69 (d, *J* = 15.5 Hz, 1H, H-3). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 14.3 ($CO_2CH_2CH_3$), 60.3 ($CO_2CH_2CH_3$), 86.9 (C-3''), 97.0 (C-1''), 111.1 (C-4'), 112.5 (C-3'), 114.1 (C-2), 123.9 (C-5'), 128.9 (C-2'), 131.7 (C-3), 167.5 (CO_2Et), 203.8 (C-2''). MS (70 eV): *m/z* 203 (43) $[M]^+$, 175 (100), 158 (30), 130 (71), 129 (47), 103 (21), 91 (10), 77 (18). HRMS (EI): *m/z* calcd. for $C_{12}H_{13}NO_2$ $[M]^+$: 203.0946; found 203.0945.

Ethyl (*E*)-3-(1-(2-Ethoxy-2-oxoethyl)-1*H*-pyrrol-2-yl)acrylate (7d): Following the method of preparation for **7a**, by using **5b** (0.050 g, 0.30 mmol), NaH (60%) (0.015 g, 0.38 mmol) and ethyl bromoacetate (**6c**) (0.061 g, 0.36 mmol) in dry DMF (1.0 mL), and after stirring at 0 ºC for 1 h, **7d** (0.075 g, 99%) was obtained as a colorless oil. R_f = 0.49 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$ = 2982, 1751, 1699, 1471, 1366, 1326, 1290, 1263, 1207, 1175, 967, 728 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (q, *J* = 7.1 Hz, 6H, 2 $CO_2CH_2CH_3$), 4.23 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.24 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.74 (s, 2H, H-1''), 6.16 (d, *J* = 15.3 Hz, 1H, H-2), 6.25 (ddd, *J* = 3.6, 2.4, 0.9 Hz, 1H, H-4'), 6.72 (dd, *J* = 3.6, 1.5 Hz, 1H, H-3'), 6.79 (dd, *J* = 1.5, 0.9 Hz, 1H, H-5'), 7.45 (d, *J* = 15.3 Hz, 1H, H-3). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 14.1 ($CO_2CH_2CH_3$), 14.3 ($CO_2CH_2CH_3$), 48.4 (C-1''), 60.2 ($CO_2CH_2CH_3$), 62.0 ($CO_2CH_2CH_3$), 110.3 (C-4'), 112.2 (C-3'), 113.8 (C-2), 126.7 (C-5'), 129.4 (C-2'), 131.5 (C-3), 167.6 (CO_2Et), 168.0 (CO_2Et). MS (70 eV): *m/z* 251 (74) $[M]^+$, 223 (5), 206 (44), 179 (32), 133 (31), 104 (100), 103 (94), 102 (61), 78 (26). HRMS (EI): *m/z* calcd. for $C_{13}H_{17}NO_4$ $[M]^+$: 251.1158; found 251.1158.

Ethyl (*E*)-3-(1-(Furan-2-carbonyl)-1*H*-pyrrol-2-yl)acrylate (7e): Following the method of preparation for **7a**, by using **5b** (0.050 g, 0.30 mmol), NaH (60%) (0.015 g, 0.38 mmol) and 2-furoyl chloride (**6d**) (0.040 g, 0.36 mmol) in dry DMF (1.0 mL), and after stirring at 0 ºC for 2.5 h, **7e** (0.069 g, 87%) was obtained as a reddish oil. R_f = 0.43 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$ = 1698, 1623, 1567, 1465, 1391, 1339, 1271, 1178, 1031, 853, 765 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.0 Hz, 3H, $CO_2CH_2CH_3$), 4.23 (q, *J* = 7.0 Hz, 2H, $CO_2CH_2CH_3$), 6.25 (d, *J* = 16.0 Hz, 1H, H-2), 6.34 (dd, *J* = 3.5, 3.0 Hz, 1H, H-4´), 6.65 (dd, *J* = 3.5, 1.5 Hz, 1H, H-4''), 6.83 (dm, *J* = 3.5 Hz, 1H, H-3'), 7.36 (dd, *J* = 3.5, 0.5 Hz, 1H, H-3''),

7.50 (dd, *J* = 3.0, 1.5 Hz, 1H, H-5'), 7.72 (dd, *J* = 1.5, 0.5 Hz, 1H, H-5''), 8.05 (d, *J* = 16.0 Hz, 1H, H-3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.3 ($CO_2CH_2\mathit{C}H_3$), 60.3 ($CO_2\mathit{C}H_2CH_3$), 112.4 (C-4'), 112.6 (C-4''), 115.5 (C-3'), 116.9 (C-2), 122.0 (C-3''), 125.4 (C-5'), 132.1 (C-2´), 134.0 (C-3), 146.4 (C-2''), 147.6 (C-5''), 156.9 (N*C*O), 166.9 (*C*O_2Et). MS (70 eV): *m/z* 259 (50) $[M]^+$, 231 (11), 203 (32), 186 (18), 158 (22), 119 (12), 95 (100), 63 (9). HRMS (EI): *m/z* calcd. for $C_{14}H_{13}NO_4$ $[M]^+$: 259.0845; found 259.0851.

Methyl (*E*)-3-(1-(Prop-2-yn-1-yl)-1*H*-pyrrol-2-yl)acrylate (8a): Following the method of preparation for **7a**, by using **5c** (0.200 g, 1.33 mmol), NaH (60%) (0.064 g, 1.59 mmol) and propargyl bromide (**6a**) (0.189 g, 1.59 mmol) in dry DMF (2.0 mL), and after stirring at 0 ºC for 1.5 h, **8a** (0.233 g, 93%) was obtained as a colorless oil. R_f = 0.70 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$ = 3243, 2951, 1690, 1622, 1468, 1331, 1286, 1173, 972, 731 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.46 (t, *J* = 2.4 Hz, 1H, H-3''), 3.78 (s, 3H, $CO_2C\mathit{H}_3$), 4.75 (d, *J* = 2.4 Hz, 2H, H-1''), 6.18 (d, *J* = 15.6 Hz, 1H, H-2), 6.20-6.23 (m, 1H, H-4'), 6.69 (dd, *J* = 3.9, 1.5 Hz, 1H, H-3'), 6.94 (dd, *J* = 2.7, 1.5 Hz, 1H, H-5'), 7.64 (d, *J* = 15.6 Hz, 1H, H-3). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 36.7 (C-1''), 51.5 ($CO_2\mathit{C}H_3$), 74.5 (C-3''), 77.3 (C-2''), 110.0 (C-4'), 112.6 (C-3'), 113.2 (C-2), 125.6 (C-5'), 128.6 (C-2'), 131.8 (C-3), 168.0 (*C*O_2Me). MS (70 eV): *m/z* 189 (17) $[M^+]$, 174 (40), 158 (43), 130 (100), 118 (11), 103 (22), 91 (14), 77 (19). Anal. calcd. for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.80; H, 5.82; N, 7.40.

Methyl (*E*)-3-(1-(Propa-1,2-dien-1-yl)-1*H*-pyrrol-2-yl)acrylate (8b): Following the method of preparation for **7a**, by using **5c** (0.100 g, 0.66 mmol), NaH (60%) (0.053 g, 1.33 mmol) and propargyl bromide (**6a**) (0.156 g, 1.33 mmol) in dry DMF (1.0 mL), and after stirring at 0 ºC for 1 h, **8b** (0.107 g, 85%) was obtained as a dark solid. R_f = 0.77 (hexane/EtOAc, 7:3); mp 54-55 °C. IR (KBr): $\overline{\nu}$ = 2924, 1704, 1622, 1460, 1436, 1263, 1168, 1030, 966, 723 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.77 (s, 3H, $CO_2C\mathit{H}_3$), 5.51 (d, *J* = 6.3 Hz, 1H, H-3''), 6.19 (d, *J* = 15.6 Hz, 1H, H-2), 6.26 (dd, *J* = 3.9, 3.0 Hz, 1H, H-4'), 6.69 (dd, *J* = 3.9, 1.5 Hz, 1H, H-3'), 6.93 (dd, *J* = 3.0, 1.5 Hz, 1H, H-5'), 7.02 (t, *J* = 6.3 Hz, 1H, H-1''), 7.69 (d, *J* = 15.6 Hz, 1H, H-3). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 51.4 ($CO_2\mathit{C}H_3$), 86.8 (C-3''), 96.8 (C-1''), 111.1 (C-4'), 112.5 (C-3'), 113.5 (C-2), 124.0 (C-5'), 128.8 (C-2'), 131.9 (C-3), 167.8 (*C*O_2CH_3), 203.8 (C-2''). MS (70 eV): *m/z* 189 (11) $[M]^+$, 158.0 (7), 130 (100), 103 (20), 77 (13). Anal. calcd. for $C_{11}H_{11}NO_2$ (189.21): C, 69.83; H, 5.86; N, 7.40. Found: C, 69.81; H, 5.86; N, 7.39.

(*E*)-3-(1-(Prop-2-yn-1-yl)-1*H*-pyrrol-2-yl)acrylonitrile (9a): Following the method of preparation for **7a**, by using **5d** (0.200 g, 1.70 mmol), NaH (60%) (0.081 g, 2.03 mmol) and propargyl bromide (**6a**) (0.242 g, 2.03 mmol) in dry DMF (2.0 mL), and after stirring at 0 ºC for 1.5 h, **9a** (0.229 g, 87%) was obtained as a colorless oil. R_f = 0.66 (hexane/EtOAc, 7:3). IR (KBr): $\overline{\nu}$ = 3237, 2208, 1608, 1470, 1412, 1295, 1085, 951, 728 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.50 (t, *J* = 2.4 Hz, 1H, H-3''), 4.71 (d, *J* = 2.4 Hz, 2H, H-1''), 5.56 (d, *J* = 16.2 Hz, 1H, H-2), 6.22 (ddd, *J* = 3.7, 2.6, 0.6 Hz, 1H, H-4'), 6.68 (dd, *J* = 3.7, 1.5 Hz, 1H, H-3'), 6.93 (dd, *J* = 2.6, 1.5 Hz, 1H, H-5'), 7.32 (d, *J* = 16.2 Hz, 1H, H-3). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 36.8 (C-1''), 74.9 (C-3''), 76.9 (C-2''), 90.6 (C-2), 110.3 (C-4'), 112.6 (C-3'), 119.3 (C-1), 126.6 (C-5'), 128.0 (C-2'), 137.0 (C-3). MS (70 eV): *m/z* 156 (40) $[M]^+$, 155 (100), 130 (18), 128 (24). Anal. calcd. for $C_{10}H_8N_2$: C, 76.90; H, 5.16; N, 17.94. Found: C, 76.86; H, 5.13; N, 17.93.

(*E*)-3-(1-(Propa-1,2-dien-1-yl)-1*H*-pyrrol-2-yl)acrylonitrile (9b): Following the method of preparation for **7a**, by using **5d** (0.100 g, 0.85 mmol), NaH (60%) (0.068 g, 1.70 mmol) and propargyl bromide (**6a**) (0.200 g, 1.70 mmol) in dry DMF (1.0 mL), and after stirring at 0 ºC for 1 h, **9b** (0.114 g, 86%) was obtained as a colorless oil. R_f = 0.74 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$ = 2925, 2209, 1610, 1463, 1410, 1320, 1134, 956, 892, 722 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.55 (d, *J* = 6.3, 1H, H-3''), 5.56 (d, *J* = 16.2 Hz, 1H, H-2), 6.27 (dd, *J* = 3.8, 2.7 Hz, 1H, H-4'), 6.67 (dd, *J* = 3.8, 1.5 Hz, 1H, H-3'), 6.91 (t, *J* = 6.3 Hz, 1H, H-1''), 6.95 (dd, *J* = 2.7, 1.5 Hz, 1H, H-5'), 7.34 (d, *J* = 16.2 Hz, 1H, H-3). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 87.0 (C-3''), 90.7 (C-2), 96.4 (C-1''), 111.2 (C-4'), 112.5 (C-3'), 119.0 (C-1), 124.8 (C-5'), 128.0 (C-2'), 137.0 (C-3), 203.7 (C-2''). MS (70 eV): *m/z* 156 (100) $[M]^+$, 155 (100), 130 (20), 128 (42), 101 (6).

Ethyl (*E*)-3-(5-Formyl-1-(prop-2-ynyl)-1*H*-pyrrol-2-yl)acrylate (10a): Dry DMF (0.043 g, 0.59 mmol) was added to phosphorus oxychloride (0.091 g, 0.59 mmol) at 0 ºC, and the resulting mixture was stirred for 10 min. Then, **7a** (0.100 g, 0.49 mmol) was added dropwise and the temperature was slowly raised to 40 °C and maintained for 2 h. The reaction mixture was quenched with an aqueous solution of NaOH 2N until neutral, CH_2Cl_2 (250 mL) was added, the organic layer dried (Na_2SO_4) and the solvent removed under vacuum. The residue was purified by column chromatography over silica gel (30 g/g crude, hexane/EtOAc, 98:2) to give **10a** (0.101 g, 88%) as a white solid. R_f = 0.59 (hexane/EtOAc, 7:3); mp 90-91 °C. IR (KBr): $\overline{\nu}$ = 1705, 1659, 1628, 1472, 1449, 1409, 1309, 1270, 1234, 1183, 1048, 783 cm'^{1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2C\mathit{H_3}$), 2.38 (t, *J* = 2.7 Hz, 1H, H-3''), 4.28 (q, *J* = 7.2 Hz, 2H, $CO_2C\mathit{H_2}CH_3$), 5.39 (d, *J* = 2.7 Hz, 2H, H-1''), 6.47 (d, *J* = 15.6 Hz, 1H, H-2), 6.70 (dd, *J* = 4.2, 0.6 Hz, 1H, H-3'), 6.96 (dd, *J* = 4.2, 0.9 Hz, 1H, H-4'), 7.72 (d, *J* = 15.6 Hz, 1H, H-3), 9.60 (s, 1H, C*H*O). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 14.3 ($CO_2CH_2\mathit{C}H_3$), 34.4 (C-1''), 60.8 ($CO_2\mathit{C}H_2CH_3$), 73.6 (C-3''), 77.7 (C-2''), 111.6 (C-3'), 121.4 (C-2), 124.7 (C-4'), 130.0 (C-3), 132.8 (C-5'), 137.5 (C-2'), 166.3 (*C*O_2Et), 179.9 (*C*HO). MS (70 eV): *m/z* 231 (M^+, 18), 203 (41), 202 (100), 174 (37), 158 (41), 130 (42), 103 (24), 77 (9). Anal. calcd. for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.52; H, 5.61; N, 6.03.

Ethyl (*E*)-3-(5-Formyl-1-(3-methylbut-2-enyl)-1*H*-pyrrol-2-yl)acrylate (10b): Following the method of preparation for

10a, by using DMF (0.038 g, 0.52 mmol), $POCl_3$ (0.080 g, 0.52 mmol) and **7b** (0.100 g, 0.43 mmol), and after stirring at 40 ºC for 2 h, **10b** (0.091 g, 81%) was obtained as a white solid. R_f = 0.34 (hexane/EtOAc, 7:3); mp 74-75 °C. IR (film): $\overline{\nu}$ = 1706, 1663, 1625, 1475, 1307, 1244, 1184, 1051, 772 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.34 (t, *J* = 6.9 Hz, 3H, $CO_2CH_2CH_3$), 1.71 (br s, 3H, H-4'' or H-5''), 1.85 (br s, 3H, H-5'' or H-4''), 4.26 (q, *J* = 6.9 Hz, 2H, $CO_2CH_2CH_3$), 5.15 (br s, 3H, H-1'', H-2''), 6.39 (d, *J* = 15.9 Hz, 1H, H-2), 6.66 (dd, *J* = 4.2, 0.6 Hz, 1H, H-3'), 6.92 (dd, *J* = 4.2, 0.6 Hz, 1H, H-4'), 7.60 (d, *J* = 15.9 Hz, 1H, H-3), 9.58 (s, 1H, CHO). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 14.3 ($CO_2CH_2CH_3$), 18.2 (C-4'' or C-5''), 25.6 (C-5'' or C-4''), 43.4 (C-1''), 60.7 ($CO_2CH_2CH_3$), 110.9 (C-3'), 120.3 (C-2), 120.4 (C-2''), 124.3 (C-4'), 130.8 (C-3), 133.3 (C-5'), 135.5 (C-3''), 137.3 (C-2'), 166.5 (CO_2Et), 179.8 (CHO). MS (70 eV): *m/z* 261 (M^+, 7), 225 (15), 202 (17), 188 (56), 167 (20), 155 (20), 148 (100), 119 (24), 73 (20). HRMS (EI): *m/z* calcd. for $C_{15}H_{19}NO_3$ $[M]^+$: 261.1365; found 261.1358.

Ethyl (*E*)-3-(5-Formyl-1-(propa-1,2-dien-1-yl)-1*H*-pyrrol-2-yl)acrylate (10c): Following the method of preparation for **10a**, by using DMF (0.086 g, 1.18 mmol), $POCl_3$ (0.181 g, 1.18 mmol) and **7c** (0.200 g, 0.99 mmol), and after stirring at 40 ºC for 2 h, **10c** (0.189 g, 83%) was obtained as a pale yellow oil. R_f = 0.34 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$ = 1709, 1660, 1445, 1370, 1261, 1190, 1036, 784 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.34 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 4.26 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 5.48 (d, *J* = 6.4 Hz, 2H, H-3''), 6.37 (d, *J* = 15.8 Hz, 1H, H-2), 6.70 (dd, *J* = 4.3, 0.6 Hz, 1H, H-3'), 7.02 (dd, *J* = 4.3, 0.6 Hz, 1H, H-4'), 7.62 (t, *J* = 6.4 Hz, 1H, H-1''), 7.83 (dd, *J* = 15.8, 0.6 Hz, 1H, H-3), 9.65 (s, 1H, CHO). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 14.2 ($CO_2CH_2CH_3$), 60.7 ($CO_2CH_2CH_3$), 85.6 (C-3''), 95.9 (C-1''), 111.8 (C-3'), 120.2 (C-2), 124.0 (C-4'), 131.8 (C-3), 133.4 (C-5'), 137.3 (C-2'), 166.4 (CO_2Et), 179.5 (CHO), 203.8 (C-2''). MS (70 eV): *m/z* 231 (46) $[M]^+$, 203 (12), 158 (100), 130 (53), 103 (27), 77 (9). HRMS (EI): *m/z* calcd. for $C_{13}H_{13}NO_3$ $[M]^+$: 231.0895; found 231.0882.

Methyl (*E*)-3-(5-Formyl-1-(propa-1,2-dien-1-yl)-1*H*-pyrrol-2-yl)acrylate (11a): Following the method of preparation for **10a**, by using DMF (0.047 g, 0.64 mmol), $POCl_3$ (0.098 g, 0.64 mmol) and **8b** (0.100 g, 0.53 mmol), and after stirring at 40 ºC for 2 h, **11a** (0.101 g, 88%) was obtained as a brown solid. R_f = 0.65 (hexane/EtOAc, 7:3); mp 88-89 ºC. IR (film): $\overline{\nu}$ = 2950, 1706, 1656, 1627, 1449, 1310, 1275, 1201, 1046, 971, 790 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.81 (s, 3H, CO_2CH_3), 5.48 (d, *J* = 6.6 Hz, 2H, H-3''), 6.37 (d, *J* = 15.6 Hz, 1H, H-2), 6.70 (d, *J* = 4.3 Hz, 1H, H-3'), 7.02 (d, *J* = 4.3 Hz, 1H, H-4'), 7.60 (t, *J* = 6.6 Hz, 1H, H-1''), 7.82 (d, *J* = 15.6 Hz, 1H, H-3), 9.65 (s, 1H, CHO). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 51.8 (CO_2CH_3), 85.5 (C-3''), 95.9 (C-1''), 111.8 (C-3'), 119.6 (C-2), 123.9 (C-4'), 132.0 (C-3), 133.5 (C-5'), 137.1 (C-2'), 166.8 (CO_2CH_3), 179.4 (CHO), 203.6 (C-2''). MS (70 eV): *m/z* 217 (42) $[M]^+$, 158 (100), 130 (37), 103 (22), 77 (11). Anal. calcd. for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: 66.30; H, 5.12; N, 6.45.

(*E*)-3-(5-Formyl-1-(prop-2-ynyl)-1*H*-pyrrol-2-yl)acrylonitrile (12a): Following the method of preparation for **10a**, by using DMF (0.056 g, 0.77 mmol), $POCl_3$ (0.118 g, 0.77 mmol) and **9a** (0.100 g, 0.64 mmol), and after stirring at 40 ºC for 2 h, **12a** (0.109 g, 92%) was obtained as a white solid. R_f = 0.51 (hexane/EtOAc, 7:3); mp 103-104 ºC. IR (film): $\overline{\nu}$ = 2213, 1662, 1614, 1452, 1412, 1236, 1213, 1051, 968, 786 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.43 (t, *J* = 2.7 Hz, 1H, H-3''), 5.38 (d, *J* = 2.7 Hz, 2H, H-1''), 5.91 (d, *J* = 16.2 Hz, 1H, H-2), 6.71 (dd, *J* = 4.4, 0.6 Hz, 1H, H-3'), 6.97 (dd, *J* = 4.4, 0.6 Hz, 1H, H-4'), 7.47 (br d, *J* = 16.2 Hz, 1H, H-3), 9.63 (s, 1H, CHO). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 34.4 (C-1''), 74.2 (C-3''), 77.3 (C-2''), 98.6 (C-2), 111.7 (C-3'), 117.7 (C-1), 124.5 (C-4'), 133.1 (C-5'), 136.1 (C-3), 136.2 (C-2'), 180.3 (CHO). MS (70 eV): *m/z* 184 (36) $[M]^+$, 156 (34), 155 (100), 138 (34), 128 (29). HRMS (EI): *m/z* calcd. for $C_{11}H_8N_2O$ $[M]^+$: 184.0637; found 184.0637.

(*E*)-3-(5-Formyl-1-(propa-1,2-dien-1-yl)-1*H*-pyrrol-2-yl)acrylonitrile (12b): Following the method of preparation for **10a**, by using DMF (0.112 g, 1.54 mmol), $POCl_3$ (0.236 g, 1.54 mmol) and **9b** (0.200 g, 1.28 mmol), and after stirring at 40 ºC for 2 h, **12b** (0.175 g, 75%) was obtained as a colorless oil. R_f = 0.32 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$ = 2922, 2207, 1607, 1458, 1412, 1303, 1079, 951, 731 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.51 (d, *J* = 6.6 Hz, 2H, H-3''), 5.81 (d, *J* = 16.5 Hz, 1H, H-2), 6.70 (br d, *J* = 4.2 Hz, 1H, H-3'), 7.03 (dd, *J* = 4.2, 0.6 Hz, 1H, H-4'), 7.50 (dt, *J* = 16.5, 0.6 Hz, 1H, H-3), 7.59 (t, *J* = 6.6 Hz, 1H, H-1''), 9.68 (s, 1H, CHO). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 85.9 (C-3''), 95.7 (C-1''), 97.4 (C-2), 111.9 (C-3'), 117.8 (C-1), 123.7 (C-4'), 133.8 (C-5'), 135.8 (C-2'), 137.4 (C-3), 179.7 (CHO), 206.3 (C-2''). MS (70 eV): *m/z* 184 (70) $[M]^+$, 156 (100), 128 (30). HRMS (EI): *m/z* calcd. for $C_{11}H_8N_2O$ $[M]^+$: 184.0637; found 184.0635.

4-(Hydroxymethyl)phenyl 4-Methylbenzenesulfonate (18): Triethylamine (0.829 g, 8.19 mmol) was added to a mixture of 4-hydroxybenzaldehyde (**17**) (0.500 g, 4.09 mmol) and DMAP (0.050 g, 0.41 mmol) in CH_2Cl_2 (15 mL), which was stirred at room temperature for 20 min. *p*-Toluenesulfonyl chloride (1.171 g, 6.14 mmol) was added at 0 °C and the mixture was stirred for 1.5 h. The solvent was removed under vacuum, the residue was dissolved in MeOH (10 mL) and $NaBH_4$ (0.080 g, 2.05 mmol) was added at 0 °C. The reaction mixture was stirred at the same temperature for 2 h. The solvent was removed under vacuum and the residue purified by column chromatography over silica gel (10 g/g crude, hexane/EtOAc, 1:1) to give **18** (1.187 g, 77%) as a pale yellow oil. R_f = 0.17 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$ = 3368, 2925, 1597, 1502, 1369, 1197, 1174, 1150, 1092, 1015, 865, 814, 691 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.20 (br, 1H, OH), 2.44 (s, 3H, CH_3), 4.63 (s, 2H, CH_2), 6.94 (d, *J* = 8.8 Hz, 2H, H-2'), 7.25 (d, *J* = 8.8 Hz, 2H, H-3'), 7.29 (d, *J* = 8.0 Hz, 2H, H-3), 7.68 (d, *J* = 8.0 Hz, 2H,

H-2). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.6 (*C*H$_3$), 64.2 (*C*H$_2$), 122.3 (C-2'), 127.9 (C-3'), 128.4 (C-2), 129.7 (C-3), 132.2 (C-1), 139.8 (C-4'), 145.4 (C-4), 148.8 (C-1'). MS (70 eV): *m/z* 278 (40) [M$^+$], 155 (54), 139 (10), 123 (31), 107 (46), 91 (100), 77 (10). HRMS (EI): *m/z* calcd. for $C_{14}H_{14}O_4S$ [M]$^+$: 278.0613; found 278.0604.

4-(Bromomethyl)phenyl 4-Methylbenzenesulfonate (19): Triphenylphosphine (0.860 g, 3.80 mmol) was added to a solution of **18** (0.760 g, 2.73 mmol) in CH_2Cl_2 (20 mL). After stirring at room temperature for 10 min, NBS (0.580 g, 3.28 mmol) was added at 0 °C, and the mixture was stirred at this temperature for 1 h. The solvent was removed under vacuum and the residue purified by column chromatography over silica gel (10 g/g crude, hexane/EtOAc, 95:5) to afford **19** (0.876 g, 94%) as a white solid. R_f = 0.63 (hexane/EtOAc, 7:3); mp 78-79 °C. IR (KBr): $\bar{\nu}$ = 3401, 2918, 1806, 1596, 1500, 1369, 1197, 1177, 1147, 1091, 1018, 859, 810, 742, 695 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.44 (s, 3H, C*H*$_3$), 4.42 (s, 2H, C*H*$_2$), 6.95 (d, *J* = 8.5 Hz, 2H, H-2'), 7.28-7.33 (m, 4H, H-3', H-3), 7.70 (d, *J* = 8.0 Hz, 2H, H-2). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.7 (*C*H$_3$), 32.1 (*C*H$_2$), 122.7 (C-2'), 128.4 (C-2), 129.8 (C-3), 130.3 (C-3'), 132.3 (C-1), 136.7 (C-4'), 145.5 (C-4), 149.3 (C-1'). MS (70 eV): *m/z* 341 (2) [M$^+$], 261 (81), 155 (100), 91 (77). HRMS (EI): *m/z* calcd. for $C_{14}H_{13}BrO_3S$ [M]$^+$: 339.9769; found 339.9759.

4-((2-Formyl-1*H*-pyrrol-1-yl)methyl)phenyl 4-Methylbenzenesulfonate (20): According to the method for the preparation of **7a**, by using 2-formylpyrrol (**5a**) (0.558 g, 5.86 mmol), NaH (60%) (0.281 g, 7.03 mmol) and compound **19** (2.00 g, 5.86 mmol) in dry DMF (10 mL), and after stirring at 25 ºC for 5 h, **20** (2.001 g, 96%) was obtained as a white resin. R_f = 0.38 (hexane/EtOAc, 7:3). IR (film): $\bar{\nu}$ = 1662, 1597, 1503, 1477, 1404, 1371, 1319, 1198, 1177, 1154, 1092, 867, 757, 720 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.43 (s, 3H, C*H*$_3$), 5.50 (s, 2H, C*H*$_2$), 6.27 (t, *J* = 3.6 Hz, 1H, H-4''), 6.86-6.92 (m, 2H, H-2'), 6.96 (d, *J* = 3.6 Hz, 2H, H-3'', H-5''), 7.01-7.07 (m, 2H, H-3'), 7.25-7.32 (m, 2H, H-3), 7.63-7.69 (m, 2H, H-2), 9.50 (d, *J* = 0.6 Hz, 1H, C*H*O). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.6 (*C*H$_3$), 51.0 (*C*H$_2$), 110.3 (C-4''), 122.4 (C-2'), 125.0 (C-3''), 128.2 (C-3'), 128.3 (C-2), 129.7 (C-3), 131.1 (C-2''), 131.4 (C-5''), 132.0 (C-1), 136.6 (C-4'), 145.4 (C-4), 148.8 (C-1'), 179.4 (*C*HO). MS (70 eV): *m/z* 355 (27) [M]$^+$, 337 (8), 261 (14), 200 (94), 155 (54), 107 (32), 94 (100), 91 (38).

4-((2-(Hydroxymethyl)-1*H*-pyrrol-1-yl)methyl)phenyl 4-Methylbenzenesulfonate (21): $NaBH_4$ (0.099 g, 2.62 mmol) was added to a solution of **20** (1.860 g, 5.23 mmol) in a mixture of MeOH/CH_2Cl_2 (1:1) (20 mL) at 0 °C, and the mixture was stirred at this temperature for 2 h. The solvent was removed under vacuum and the crude product purified by column chromatography over silica gel (20 g/g crude, hexane/EtOAc, 7:3) to afford **21** (1.777 g, 95%) as a colorless oil. R_f = 0.25 (hexane/EtOAc, 7:3). IR (film): $\bar{\nu}$ = 3375, 2924, 1596, 1501, 1367, 1298, 1196, 1174, 1150, 1091, 1016, 862, 715 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.51 (br s, 1H, OH), 2.44 (s, 3H, C*H*$_3$), 4.45 (br s, 2H, C*H*$_2$OH), 5.15 (s, 2H, H-1''), 6.11 (dd, *J* = 3.5, 2.7 Hz, 1H, H-4'''), 6.15 (dd, *J* = 3.5, 1.8 Hz, 1H, H-3'''), 6.65 (dd, *J* = 2.7, 1.8 Hz, 1H, H-5'''), 6.86-6.97 (m, 4H, H-2', H-3'), 7.26-7.33 (m, 2H, H-3), 7.65-7.71 (m, 2H, H-2). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 21.7 (*C*H$_3$), 49.7 (C-1''), 56.6 (*C*H$_2$OH), 107.5 (C-4'''), 109.5 (C-3'''), 122.6 (C-2'), 123.1 (C-5'''), 127.7 (C-3'), 128.4 (C-2), 129.7 (C-3), 131.6 (C-2'''), 132.1 (C-1), 137.3 (C-4'), 145.4 (C-4), 148.7 (C-1'). HRMS (EI): *m/z* calcd. for $C_{19}H_{19}NO_4S$ [M]$^+$: 357.1035; found 357.1025.

(1-(4-(*p*-Tosyloxy)benzyl)-1*H*-pyrrol-2-yl)methyl acetate (22): Pyridine (0.806 g, 10.19 mmol) was added to a solution of **21** (1.821 g, 5.09 mmol) in dry CH_2Cl_2 (30 mL) at 0 °C. After stirring for 30 min, acetic anhydride (1.048 g, 10.19 mmol) was added and the mixture was stirred at room temperature for 24 h, followed by washing with water (100 mL) and an aqueous solution of HCl 5% until neutral. The aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (20 g/g crude, hexane/EtOAc, 8:2) to give **22** (1.974 g, 97%) as a yellow oil. R_f = 0.48 (hexane/EtOAc, 7:3). IR (film): $\bar{\nu}$ = 2926, 1735, 1596, 1502, 1372, 1302, 1237, 1197, 1176, 1152, 1092, 1017, 864, 834, 815, 719 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.80 (s, 3H, C*H*$_3$CO$_2$), 2.45 (s, 3H, C*H*$_3$), 4.97 (s, 2H, C*H*$_2$), 5.09 (s, 2H, H-1''), 6.16 (dd, *J* = 3.5, 2.8 Hz, 1H, H-4'), 6.29 (dd, *J* = 3.5, 1.8 Hz, 1H, H-3'), 6.70 (dd, *J* = 2.8, 1.8 Hz, 1H, H-5'), 6.85-6.95 (m, 4H, H-2''', H-3'''), 7.28-7.34 (m, 2H, H-3^{IV}), 7.66-7.72 (m, 2H, H-2^{IV}). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 20.7 (*C*H$_3$CO$_2$), 21.7 (*C*H$_3$), 49.8 (C-1''), 57.4 (*C*H$_2$), 108.0 (C-4'), 112.0 (C-3'), 122.6 (C-3'''), 123.7 (C-5'), 126.6 (C-2'), 127.3 (C-2'''), 128.4 (C-2^{IV}), 129.8 (C-3^{IV}), 132.2 (C-1^{IV}), 137.2 (C-1'''), 145.4 (C-4^{IV}), 148.7 (C-4'''), 170.6 (CH$_3$*C*O$_2$). MS (70 eV): *m/z* 341 (14) [M - 59]$^+$, 261 (13), 203 (17), 184 (15), 155 (22), 124 (20), 107 (24), 91 (100), 77 (25). HRMS (EI): *m/z* calcd. for $C_{21}H_{21}NO_5S$ [M]$^+$: 399.1140; found 399.1129.

(5-Formyl-1-(4-(*p*-tosyloxy)benzyl)-1*H*-pyrrol-2-yl)methyl acetate (23): Following the method of preparation for **7a**, by using dry DMF (0.137 g, 1.87 mmol), $POCl_3$ (0.287 g, 1.87 mmol) and **22** (0.680 g, 1.70 mmol) in dry DMF (6.0 mL), and after stirring at 0 ºC for 30 min, the reaction mixture was quenched with an aqueous solution of KOH 1M (30 mL) and extracted with EtOAc (2 x 100 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (20 g/g crude, hexane/EtOAc, 8:2) to give **23** (0.209 g, 57%) as a pale yellow resin. R_f = 0.63 (hexane/EtOAc, 1:1). IR (film): $\bar{\nu}$ = 1741, 1663, 1503, 1371, 1225, 1198, 1176, 1153, 1092, 1019, 865 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.84 (s, 3H, C*H*$_3$CO$_2$), 2.45 (s, 3H, C*H*$_3$), 5.00 (s, 2H, C*H*$_2$), 5.64 (s, 2H, H-1''), 6.49 (d, *J* = 4.0 Hz, 1H, H-3'), 6.83-6.88 (m, 2H, H-3'''), 6.88-6.93 (m, 2H, H-2'''), 6.97 (d, *J* = 4.0 Hz, 1H, H-4'),

7.28-7.32 (m, 2H, H-3^{IV}), 7.67-7.98 (m, 2H, H-2^{IV}), 9.55 (s, 1H, C*H*O). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.5 (*C*H_3CO_2), 21.7 (*C*H_3), 48.0 (C-1''), 56.7 (*C*H_2), 112.9 (C-3'), 122.5 (C-3'''), 124.2 (C-4'), 127.2 (C-2'''), 128.4 (C-2^{IV}), 129.8 (C-3^{IV}), 132.4 (C-1^{IV}), 132.8 (C-5'), 136.6 (C-1'''), 137.0 (C-2'); 145.4 (C-4^{IV}), 148.8 (C-4'''), 170.2 (CHO), 179.8 (CH$_3$*C*O$_2$). MS (70 eV): *m/z* 427 (3) $[M]^+$, 367 (11), 272 (9), 261 (9), 212 (100), 196 (17), 184 (24), 155 (52), 123 (38), 108 (11), 91 (27). HRMS (EI): *m/z* calcd. for $C_{22}H_{21}NO_6S$ $[M]^+$: 427.1090; found 427.1089.

1-(4-Hydroxybenzyl)-5-(hydroxymethyl)-1*H*-pyrrole-2-carbaldehyde (Pyrrolemarumine) (4b) [10]**:** A mixture of compound **23** (0.167 g, 0.39 mmol) and KOH (0.088 g, 1.56 mmol) in a mixture of MeOH/H_2O (1:1) (3 mL) was stirred at room temperature for 24 h. MeOH was removed under vacuum and CH_2Cl_2 (50 mL) was added. The mixture was washed with water (50 mL) and an aqueous solution of HCl 5% until neutral. The aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The organic layers were dried (Na_2SO_4) and the solvent removed under vacuum. The residue was purified by column chromatography over silica gel (20 g/g crude, hexane/EtOAc, 1:1) to afford **4b** (0.069 g, 76%) as a pale yellow resin. R_f = 0.35 (hexane/EtOAc, 1:1). IR (film): $\bar{\nu}$ = 3333, 2970, 1644, 1516, 1456, 1371, 1243, 1173, 1046, 1011, 822, 784, cm^{-1}. ^{1}H NMR (300 MHz, acetone-d_6): δ = 4.48 (br s, 1H, CH_2OH), 4.57 (br s, 2H, CH_2OH), 5.65 (s, 2H, H-1'), 6.27 (d, *J* = 3.9 Hz, 1H, H-4), 6.71-6.78 (m, 2H, H-3''), 6.89-6.96 (m, 2H, H-2''), 6.98 (d, *J* = 3.9 Hz, 1H, H-3), 8.43 (br s, 1H, Ar-O*H*), 6.53 (s, 1H, C*H*O). ^{13}C NMR (75.4 MHz, acetone-d_6): δ = 48.3 (C-1'), 56.7 (*C*H_2OH), 110.7 (C-4), 116.1 (C-3''), 124.8 (C-3), 128.7 (C-2''), 130.0 (C-1''), 133.3 (C-2), 144.4 (C-5), 157.5 (C-4''), 180.0 (*C*HO). MS (70 eV): *m/z* 231 (11) $[M]^+$, 214 (11), 125 (100), 108 (82), 107 (80), 96 (48), 77 (39), 68 (18). DART-MS *m/z* calcd. for $C_{13}H_{14}NO_3$ $[M + H]^+$: 232.0967; found: 232.0974.

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A Quantum Mechanical Analysis of the Electronic Response of BN Nanocluster to Formaldehyde

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Abstract. It has been previously demonstrated that the electronic properties of pristine BN nanotubes and graphene-like sheets are not sensitive toward presence of H_2CO gas. Here, the adsorption of H_2CO on the external surface of $B_{12}N_{12}$ nano-cage is studied using X3LYP and Minnesota density functional calculations. Three different adsorption behaviors were found including physisorption, chemisorption, and chemical functionalization. Gibbs free energy changes at room temperature and 1 atm pressure is in the range of -0.07 to -2.00 eV (X3LYP). The HOMO-LUMO energy gap of the cluster dramatically decreases after the H_2CO chemisorption. Thus, $B_{12}N_{12}$ nanocluster may be used in gas sensor devices for H_2CO detection.
Keywords: Nanostructures; Surfaces; Ab initio calculations; Electronic structure.

Resumen. Se ha demostrado previamente que las propiedades electrónicas de nanotubos y sábanas tipo grafeno BN prístinos no son sensibles a la presencia de H_2CO gaseoso. Aquí se estudia la adsorción de H_2CO sobre la superficie externa de nano-cajas $B_{12}N_{12}$ utilizando cálculo de funcionales de la densidad X3LYP y desarrollados en Minnesota. Se encontraron tres comportamientos de adsorción diferentes incluyendo fisisorción, quimisorción y funcionalización química. Los cambios de energía libre de Gibbs, a temperatura ambiente y presión de 1 atm, se encuentran en el rango de -0.07 a -2.00 eV (X3LYP). La brecha de energía HOMO-LUMO del cúmulo disminuye dramáticamente después de la quimisorción de H_2CO. Por lo tanto, los nano-cúmulos $B_{12}N_{12}$ podrían usarse en dispositivos sensores de gases para la detección de H_2CO.
Palabras clave: Nanoestructuras; Superficies; cálculos ab-initio; Estructura electrónica.

1. Introduction

Formaldehyde (H_2CO) is an important reactive intermediate product in tropospheric hydrocarbon oxidation initiated by the OH radical. Its concentration in the atmosphere is in the range of 1 to 10 ppb [1]. The importance of H_2CO molecule originates from its widely use in many industrial manufacturing processes due to the high chemical reactivity and good thermal stability. On the other hand, it is a well-known pollutant that is emitted through incomplete combustion processes [2]. To date, several methods have been developed to detect the H_2CO concentrations which have been reviewed comprehensively by Vairavamurthy *et al.* [3-7]. Since the discovery of fullerenes, numerous studies have been focused on the nanotubes, nanoclusters, nanocones, nanocapsules, nanoribbons, etc [8-16]. BN nanostructures are wide band gap materials, expecting to show special electronic, optical and magnetic properties such as Coulomb blockade and supermagnetism [17]. The properties of BN fullerenes are different with those of carbon fullerenes, from the viewpoint of electronic properties and thermal resistance. Geometries and stability of $(BN)_n$ (n = 4-30) nano-cages have been previously studied by various research groups [18-20]. $B_{12}N_{12}$ cluster was theoretically shown to be more stable with the structure based on decoration of truncated octahedrons in which all B vertices remain equivalent, as well as all N, and was successfully synthesized [18].

Recently, Wu *et al.* have investigated hydrogenation of a $B_{12}N_{12}$ molecule by calculations using ab initio molecular orbital theory [21]. We have previously shown [22] that $B_{12}N_{12}$ is the most stable nanocluster among different $X_{12}Y_{12}$ (X = Al or B and Y = N or P) cages. Nanostructured materials have been invoked more attention as chemical sensors due to high surface to volume ratio and high electronic sensitivity [23-29]. It has been previously demonstrated that the electronic properties of pristine BN nanotubes and graphene-like sheets are not sensitive toward presence of H_2CO gas, and cannot be used as chemical sensors [29, 30]. Here, the interaction between an H_2CO molecule and a $B_{12}N_{12}$ nanocluster is investigated using density functional theory (DFT) calculations to answer this question that whether there is a potential possibility of BN nanoclusters serving as chemical sensor to H_2CO.

2. Computational methods

Geometry optimizations, natural bond orbitals (NBO), and density of states (DOS) analyses were performed on a $B_{12}N_{12}$ nanocluster and different $H_2CO/B_{12}N_{12}$ complexes at the spin unrestricted X3LYP level [31] of theory with 6-31G (d) basis set [32] as implemented in GAMESS suite of program [33]. GaussSum program [34] was used to obtain DOS results.

Vibrational frequency calculations were performed using numerical second derivatives, verifying that all the structures are true minima with positive Hessian eigenvalues. The Gibbs free energy change (ΔG) of H_2CO adsorption at room temperature and 1 atm pressure is defined as follows:

$$\Delta G = G(H_2CO/\ B_{12}N_{12}) - G(B_{12}N_{12}) - G(H_2CO) \quad (1)$$

where $G(H_2CO/B_{12}N_{12})$ is the Gibbs free energy of complex, and $G(B_{12}N_{12})$ and $G(H_2CO)$ are the Gibbs free energies of the pristine $B_{12}N_{12}$ and H_2CO molecule, respectively. Zero-point and basis set superposition error (BSSE) corrections were included in the ΔG calculations. HOMO-LUMO energy gap (E_g) is defined as

$$E_g = E_{LUMO}\text{-}E_{HOMO} \quad (2)$$

where E_{LUMO} and E_{HOMO} are energies of HOMO and LUMO. When we evaluate the properties of the sensor, the shift of the E_g is obtained by:

$$\Delta E_g = [(E_{g2} - E_{g1})/E_{g1}] * 100\ \% \quad (3)$$

where E_{g1} and E_{g2} are, the value of the E_g for clean $B_{12}N_{12}$ and the formaldehyde adsorbed state, respectively.

3. Results and discussion

The $B_{12}N_{12}$ (Fig. 1) nanocluster is made of six squares and eight hexagons. There are two types of individual B–N bond among the all 36 B–N bonds; one is shared by two six-membered rings (B_{66}), and another by a four- and a six-membered ring (B_{64}). The B_{64} bond (average length = 1.48 Å) is somewhat longer than the B_{66} one (average length = 1.43 Å). NBO population analysis shows a net charge transfer of 0.45 electrons from B to N atom in the surface of the cluster, indicating partly ionic nature of these bonds. Several distinct starting structures were considered for H_2CO adsorption on the cluster. For example, the oxygen or a hydrogen atom of H_2CO molecule was placed atop a hexagon or a square ring, or the molecule was located close to B_{64} or B_{66} bond so that its O and C or H atoms were close to the B and N atoms of these bonds. However, after careful relax optimization of initial structures four different stable structures (local minima) were obtained which are shown in Figs. 2-4.

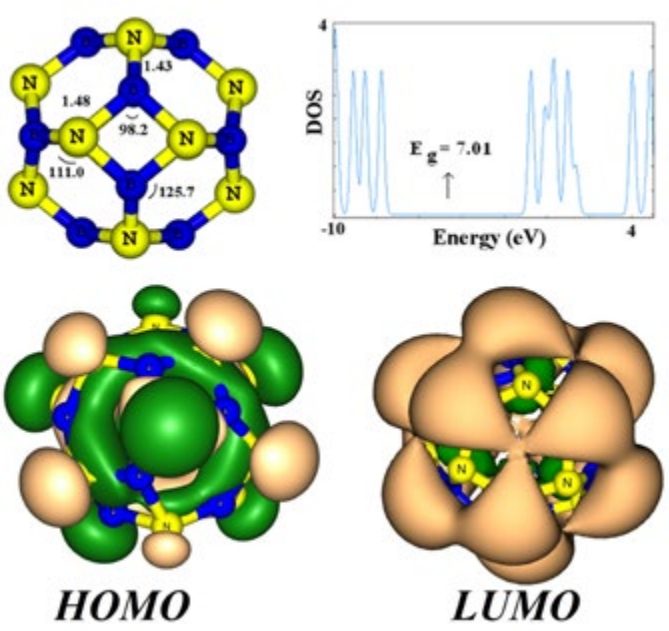

Fig. 1. Structural model, HOMO, LUMO profiles and the electronic density of states (DOS) of the $B_{12}N_{12}$ cluster. (Bonds are in angstrom and angles are in degree).

The interactions can be divided into three types: (I) Physisorption, in which H_2CO molecule weakly interacts with the cluster through van der Waals forces and less negative ΔG values (configurations **A**, Fig. 2). (II) Chemisorption, in which the ΔG value is rather more negative than that of the physisorption, and an insignificant change occurs in the geometrical parameters (configuration **B**, Fig. 3). (III) Chemical functionalization, including very strong interaction that largely deforms the structure of the cluster with bond cleavages and formations (configurations **C** and **D**, Fig. 4). The ΔG values, charge transfer, and electronic properties for the all configurations are summarized in Table 1. For the physisorption configuration **A**, the calculated values of ΔG is about -0.07 eV. Also, the corresponding interaction distances between the N atom of $B_{12}N_{12}$ cluster and the H atom of H_2CO molecule is 3.30 Å. The less negative ΔG values and large interaction distances indicate that the H_2CO molecule undergoes a weak physical adsorption due to van der

Table 1. Calculated Gibss free energy change (ΔG), HOMO energies (E_{HOMO}), LUMO energies**,** HOMO-LUMO energy gap (E_g), and Fermi level energy (E_F) of formaldehyde adsorbed on the $B_{12}N_{12}$. Energies are in eV. See Figs. 2, 3 and 4.

system	ΔG	LUMO	E_F	HOMO	E_g	ΔE_g (%)	[a]Q_T (|e|)
cage	-	-1.63	-5.14	-8.64	7.01	-	-
A	-0.07	-1.65	-4.77	-7.88	6.23	11	0.02
B	-0.59	-2.77	-4.59	-6.4	3.63	48	0.21
C	-2.00	-1.07	-4.23	-7.39	6.32	10	-0.04
D	-1.55	-1.09	-4.48	-7.86	6.77	3	-0.02

[a] Q_T is defined as the total NBO charge on the formaldehyde

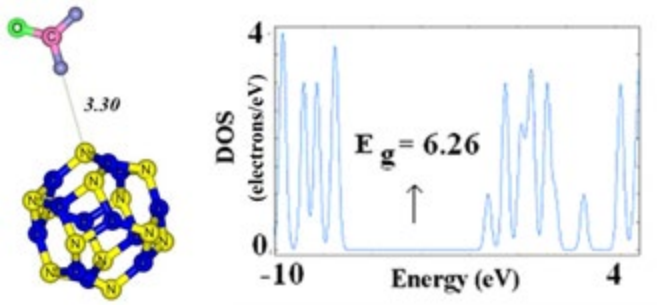

Fig. 2. The optimized structures of H_2CO physisorption on the $B_{12}N_{12}$ cluster and their DOSs.

Waals forces. The DOS for this configuration is shown in Fig. 2. It can be found that the DOS of pristine BN cluster (Fig. 1) is slightly affected by the adsorption of H_2CO molecule near the Fermi level and ΔE_g is negligible. The charge transfer from the H_2CO molecule to the cluster is very small (about 0.02 e).

As shown in Fig. 3, the distances between the H and O atoms of H_2CO, and the N and B atoms of the cluster in the configuration **B** are about 1.66 and 2.33 Å, respectively. The ΔG value is about -0.59 eV with a charge transfer of 0.21 *e* from the H_2CO molecule to the cluster. The adsorption induces a slight structural deformation to both the adsorbed molecule and the $B_{12}N_{12}$ nanocluster (Fig. 3). Angles of H-C-H and H-C-O of H_2CO are changed from 115.2° and 122.3° in their free state to 121.5° and 119.9° in the adsorbed form, and the H_2CO-adsorbed B-N bond is pulled outward from the cluster surface with the bond length increasing from 1.43 Å (pristine cluster) to 1.50 Å. In order to explore the sensitivity of $B_{12}N_{12}$ toward H_2CO molecule, we plotted the DOS of this structure and compared it with that of free cluster.

As shown in Fig. 3, the DOSs of the configuration **B** near the conduction level has an appreciate change compared to that of the pristine cluster, so that a local energy level appears after the adsorption of H_2CO molecule. Our frontier molecular analysis shows that in consistent with the energy change the LUMO shifts on the H_2CO molecule while the HOMO is still remained on the cluster (Fig. 3). Fig. 1 indicates that in the pristine cluster the HOMO and LUMO is mainly located on the N and B atoms of the cluster, respectively. However, based on the DOS analysis, the E_g value of the cluster decreases from 7.01 to 3.63 eV (48% change) upon the H_2CO molecule chemisorption on the BN cluster, which would result in the electrical conductivity change of the cluster. This phenomenon can be interpreted by the following relation [35]:

$$\sigma = A\, T^{3/2} \exp(-E_g/2kT) \quad (4)$$

Where σ is the electrical conductivity, A (electrons/$m^3K^{3/2}$) is a constant, and k is the Boltzmann's constant. According to the equation, smaller E_g at a given temperature leads to the larger electrical conductivity. It has been previously [36] shown this equation is compatible with the experimental results, and larger E_g at a given temperature leads to smaller electrical conductivity.

However, it seems that the cluster can transform the presence of the H_2CO directly into an electrical signal, suggesting

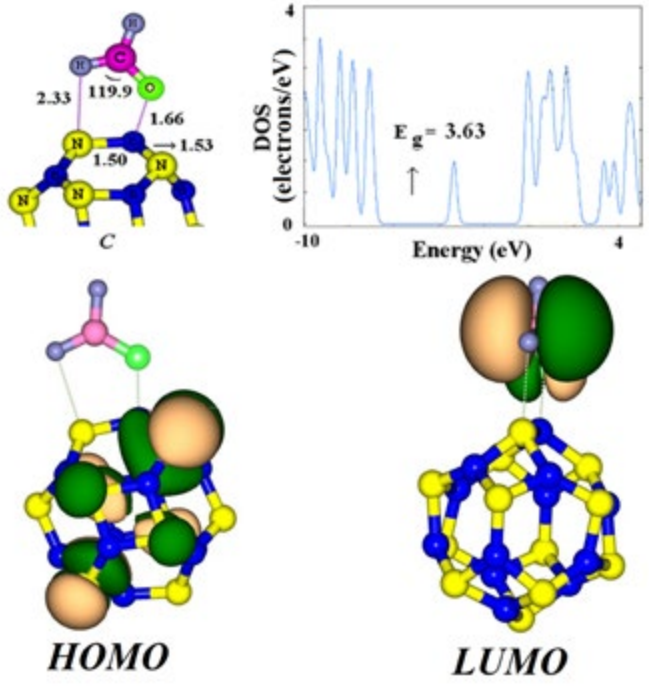

Fig. 3. The optimized structure of H_2CO chemisorption on the $B_{12}N_{12}$ cluster and its DOS plot, HOMO, and LUMO profiles.

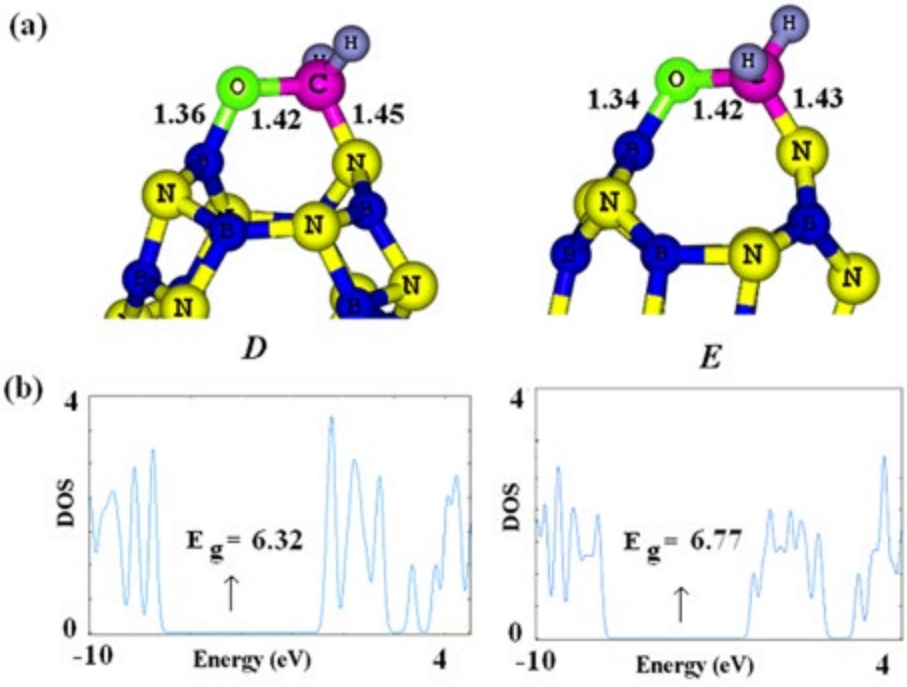

Fig. 4. The optimized structures of chemically functionalized $B_{12}N_{12}$ cluster with H_2CO and their DOSs.

that, $B_{12}N_{12}$ nanocluster may be a sensitive gas sensor toward the toxic H_2CO molecules. We found that this behavior of the BN nanocluster is in contrast to that of the BNNTs reporting by Zhang *et al*. [30]. They have theoretically investigated the adsorption of H_2CO molecule on the BNNTs, showing that the electronic properties of pristine types of these nanotubes are not affected by the adsorption of H_2CO molecule. Recovery of the sensor devices is of great importance. Based on the conventional transition state theory, the recovery time, τ, can be expressed as [36]:

$$\tau = \nu_0^{-1} \exp(-\Delta G/kT)$$

where T is temperature, k is the Boltzmann's constant, and ν_0 is the attempt frequency. According to this equation, an increase in the ΔG, will prolong the recovery time in an exponential manner.

As shown in Table 1, the ΔG of H_2CO chemisorption is about -0.59 eV which is not too large to prolong the desorption process. Finally, we considered two possible configurations that in which the cluster undergoes a strong chemical functionalization with the H_2CO molecule. To this end, the C-O bond of H_2CO molecule was horizontally located close to a B-N bond of the cluster, and then a full relax optimization was performed. The functionalized structures are shown in Fig. 4, in which the H_2CO molecule strongly adsorbed on the B_{64} (configuration **C**) or B_{66} (configuration **D**) bonds. Based on the NBO results and geometry analysis, both the B_{64} and B_{66} bonds are broken after the adsorption process and two new bonds are formed, namely, C-N and O-B. The configurations **C** and **D** have ΔG of -2.00 and -1.55 eV, with rather a small charge transfer about 0.04 and 0.02 e from the cluster to the H_2CO molecule, respectively. Geometric parameters such as the increased C-O bond length of H_2CO molecule (1.42 Å in configurations **C** and **D** compared to 1.20 Å in the isolated H_2CO), reduced H-C-H bond angle (109° as compared to 115.2° in the isolated H_2CO), and deviation of the hydrogen atoms from the original molecular plane, clearly indicate increasing p character of molecular orbitals on the C and O atoms. The NBO analysis shows that the hybridization of C and O atoms of free formaldehyde is about $sp^{2.11}$ and $sp^{1.42}$ which change to $sp^{3.14}$ and $sp^{2.85}$ in **D** configuration, respectively.

As it is shown in Table 1, the released energy during the chemical functionalization of the B_{64} bond is somewhat larger than that of the B_{66} bond. It can be interpreted by the fact that the B_{64} bond is shared by six- and four-membered rings while the B_{66} by two six-membered ones. Since a four-membered ring is thermodynamically more unstable than a six-membered one due to high strain, its cleavage is energetically easy in comparison to that of the six-membered ring, therefore, chemical functionalization of the B_{64} bond is thermodynamically more favorable than that of the B_{66} one.

The electronic properties of the cluster are not significantly changed upon the formaldehyde adsorption via these configurations. The DOS plots are shown in Fig. 4, indicating that the E_g value of cluster is slightly decreased by 0.69 and 0.24 eV in the **C** and **D** configurations, respectively. Despite the thermodynamic feasibility of the chemical functionalization, the process does not occur in room temperature due to obvious activation barriers for structure deformations. Our transition state calculations indicate that the Gibbs free energy barrier is

Table 2. Calculated HOMO, LUMO**,** and HOMO-LUMO energy gap (E_g) for $B_{12}N_{12}$ and complex of formaldehyde chemisorption as shown in Fig. 2 by Minnesota functionals (Energies in eV).

Functional	system	LUMO	HOMO	E_g	ΔE_g (%)
M06-L	$B_{12}N_{12}$	-1.25	-6.21	5.82	65.41
	Complex	-4.20	-8.18	2.01	
M06	$B_{12}N_{12}$	-0.71	-7.38	7.46	44.12
	Complex	-3.21	-9.28	4.17	
M06-2X	$B_{12}N_{12}$	0.17	-8.48	9.45	32.08
	Complex	-2.06	-11.24	6.41	
M06-HF	$B_{12}N_{12}$	1.21	-10.43	12.46	17.76
	Complex	-0.19	-6.21	10.24	

about 2.5 eV for these configurations. The chemical functionalization is not also an appropriate process for gas detection due to poor recovery of the sensor device which is subjected to a strong chemical functionalization. In spite of the all above-mentioned points, we think that the $B_{12}N_{12}$ can detect the H_2CO gaseous molecules through its chemisorption on the exterior surface of the cluster as discussed on here earlier (the configuration **B**).

It is well known that there is not any universal exchange-correlation functional for all purposes. One of the problems of the functionals is the calculation of HOMO, LUMO and E_g. However, our main quantity is the changes of E_g and not its absolute value. Here, we studied the effect of functionals on the electronic property results. To this aim, we repeated the calculations for the complex **B** (Fig. 2) with four Minnesota functionals M06-L [37], M06 [38], M06-2X [38], and M06-HF [39] with 0, 27, 54, and 100% Hartree Fock (HF) exchange, respectively. As shown in Table 2, the energy of HOMO, LUMO and E_g is strongly depends on the kind of functional but all functionals show significant change of E_g upon adsorption of formaldehyde which is responsible to the detection process. By increasing the percentage of HF exchange the LUMO and HOMO shift up and down, respectively, thereby increasing the E_g. Also, we have investigated the effect of basis set on the results of ΔG by repeating the calculations for the complex **B** at X3LYP level with basis sets 6-31+G(d), 6-31++G(d, p), and 6-311++G(d, p). The corresponding calculated ΔG values (Zero point and BSSE corrected) are about -0.54, -0.53, and -0.51 eV, respectively, indicating that enlarging the basis set slightly affects the results.

It should be noted that there is a difference between E_g and band gap. Band gap is defined as the energy difference between the top of the valence band and the bottom of the conduction band in the solid state, but the E_g is defined in molecular level. Matxain *et al.* [40] have shown that when $B_{12}N_{12}$ monomers form a solid structure with periodic arrangement, the band gap is somewhat smaller than the E_g of an isolated cluster. Using the generalized gradient approximation (GGA), within the Perdew-Burke-Ernzerhof (PBE) functional, they predicted that the E_g of an isolated $B_{12}N_{12}$ cluster is about 6.78 eV, while the band gap of the solid state is about 5.20 eV. This indicates that although the band gap of solid state is somewhat smaller than the E_g of the isolated $B_{12}N_{12}$ monomer, it is still large indicating semiconducting character of the solid structure.

4. Conclusion

We have studied the H_2CO adsorption on the exterior surface of $B_{12}N_{12}$ nanoclusuter, using DFT calculations. It was found that the formaldehyde can be adsorbed on the cluster surface through three different ways including physisorption, chemisorption, and chemical functionalization, with ΔG in the range of -0.07 to -2.00 eV. We showed that the electrical conductivity of the cluster is dramatically changed upon the adsorption of H_2CO molecule. Therefore, it is inferred that the $B_{12}N_{12}$ nanocluster may be a potential gas sensor for detection of H_2CO molecule.

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(3*S*)-7-Hydroxy-2',3',4',5',8-pentamethoxyisoflavan (1). Amorphous powder: mp 125-126ºC; $[\alpha]_D$ + 3.12 (*c* 0.320, MeOH); UV (MeOH) λ_{max} (log ε) 218 (3.91); 284 (2.89) nm; CD (*c* 0.0136, MeOH): $[\theta]_{210}$ -2.699, $[\theta]_{226}$ 0.4130, $[\theta]_{256}$ -0.8567, $[\theta]_{285.5}$ -0.6865; IR ($CHCl_3$) ν_{max} 3530, 2939, 2840, 1603, 1494, 1193, 1040 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.72 (1H, dd, $J_{5,6}$ = 8.5, $J_{4\alpha,5}$ = 1.0 Hz, H-5), 6.53 (1H, dd, $J_{5,6}$ = 8.5 Hz, H-6), 6.40 (1H, s, H-6'), 5.80 (1H, brs, O*H*), 4.39 (1H, ddd, $J_{2\beta,2\alpha}$ = 10.5, $J_{2\beta,3\beta}$ = 3.5, $J_{2\beta,4\beta}$ = 1.0 Hz, H-2β), 4.05 (1H, dd, $J_{2\alpha,2\alpha}$ = $J_{2\alpha,3\beta}$ 10.5 Hz, H-2α), 3.95 (3H, s, CH_3O-C-3'), 3.92 (3H, s, CH_3O-C-8), 3.89 (3H, s, CH_3O-C-4'), 3.83 (3H, s, CH_3O-C-2'), 3.79 (3H, s, CH_3O-C-5'), 3.61 (1H, dddd, *J* = 10.5, 3.5, 5.5, 10.5 Hz, H-3), 2.96 (1H, ddd, $J_{4\alpha,4\beta}$ = 16.0, $J_{4\alpha,3\beta}$ = 10.5, $J_{4\alpha,5}$ = 1.0 Hz, H-4α), 2.90 (1H, ddd, *J* = 16.0, $J_{3\beta,4\beta}$ = 5.5, $J_{2\beta,4\beta}$ = 1.0 Hz, H-4β); ^{13}C NMR ($CDCl_3$, 125 MHz, assignments by APT and HMQC) δ 149.67 (C-5'), 147.60 (C-7), 147.15 (C-3'), 147.12 (C-8a), 145.50 (C-2'), 141.95 (C-4'), 134.80 (C-8), 128.90 (C-1'), 124.20 (C-5), 115.00 (C-4a), 107.10 (C-6), 70.28 (C-2), 61.89 (OCH_3-C-4'), 61.51 (OCH_3-C-2'), 61.00 (OCH_3-C-3'), 60.90 (OCH_3-C-8), 56.25 (OCH_3-C-5'), 31.84 (C-3), 31.32 (C-4); EIMS *m/z* (rel. int.): 376 $[M]^+$ (73), 224 (100), 209 (42), 152 (16), 151 (38), 121 (14). *Anal.* C 63.65%, H 6.68%, calcd for $C_{20}H_{24}O_7$, C 63.82%, H 6.43%.;

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