SÍNTESIS DE GERANIL ESTERES CATALIZADA POR $Gd(OTf)_3$ Y ESTUDIO DE LA CICLACIÓN INTRAMOLECULAR RADICALARIA DE SUS EPÓXIDOS MEDIADA POR TITANOCENO(III).

WILLIAM HERNÁN GARCÍA SANTOS

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WILLIAM HERNÁN GARCÍA SANTOS

Trabajo de grado presentado como requisito para optar el título de Químico

Director
VLADÍMIR V. KOUZNETSOV,
Químico, Pd.D, DSC.

Codirector:
CARLOS EDUARDO PUERTO GALVIS
Químico, *BSC, MS.c*.

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Titulo: SÍNTESIS DE GERANIL ESTERES CATALIZADA POR Gd(OTf)$_3$ Y ESTUDIO DE LA CICLACIÓN INTRAMOLECULAR RADICALARIA DE SUS EPÓXIDOS MEDIADA POR TITANOCENO(III).[*]

Autor: GARCIA SANTOS, William Hernán[**]

Palabras clave: Aceite esencial, Esterificación, Reacción de Prilezhaev, Ciclación intramolecular

Contenido: Los Aceites esenciales (AE), son extraídos de diferentes partes de las plantas y se encuentran constituidos por un gran número de compuestos orgánicos denominados metabolitos, esta amplia gama de especies representan para la Química Orgánica un punto de partida renovable importante en la búsqueda de nuevos bloques estructurales que permitan la obtención de compuestos con actividades biológicas sobresalientes.

El interés del Laboratorio de Química Orgánica y Biomolecular en desarrollar protocolos sintéticos en donde la implementación de los AE permitan la obtención de moléculas con actividades antioxidantes y de forma simultánea correspondan a un uso racional de la biomasa, nos ha llevado a utilizar el geraniol encontrado en el AE de la palmarosa (*Cymbopogon martinii*), en la síntesis de una pequeña librería de moléculas con promisoria actividad biológica.

Utilizando algunos ácidos carboxílicos, y una nueva metodología desarrollada por el laboratorio basada en la síntesis de Garegg-Samuelson, fue posible obtener una serie de esteres derivados del geraniol, estos fueron sometidos a protocolos oxidantes descritos en la literatura que nos permitieron obtener epóxidos regioselectivos de los esteres preparados, de igual forma se utilizaron estos compuestos sintetizados en reacciones promovidas por el cloruro de titanoceno para la obtención de una serie de (8-hidroxi-9,9-dimetil-5-metilenciclohexil)metil esteres derivados del geraniol, a los cuales se les evaluaron sus actividades antioxidantes.

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[*] Trabajo de grado

[**] Facultad de Ciencias. Escuela de Química. Director: Director: VLADÍMIR V. KOUZNETSOV, *Codirector:* CARLOS EDUARDO PUERTO GALVIS

ABSTRACT

Title: Gd(OTf)$_3$-Catalyzed the Synthesis of Geranyl Esters for the Intramolecular Radical Cyclization of their Epoxides Mediated by Titanocene(III)*

Author: GARCIA SANTOS, William Hernán**

Key words: Essential oil, Esterification, Prilezhaev reaction intramolecular cyclization.

Content: Essential oils (EO), are extracted from different parts of plants and are constituted by a large number of organic compounds named as metabolites, this huge variety of species represents an important and renewable start point for organic chemistry in the finding of new structural blocks which allow obtain compounds whit important biological activity.

The interest of the Laboratorio de Química Orgánica y Biomolecular in develop new synthetics protocols in where the implementation of EO allow the obtaining of molecules whit antioxidants activities and in the same time come into a rational use of biomass, has led us to use the geraniol found in palmarosa's EO (*Cymbopogon martini*), in the synthesis of a small library of molecules whit promising biological activities.

Using different carboxylic acids, and a new methodology developed bay our laboratory based in the synthesis of Garegg-Sammuelson was possible obtain a series of esters derivate from geraniol, this compounds was submitted to an oxidant protocol described on literature which allow us obtain regioselective epoxides of the previously prepared esters, in the same way these compounds was implemented in a promoted reaction by titanocenum chloride in the obtain of a series of (8-hydroxy-9,9-dimethyl-5-methylene cyclohexyl)methyl esters derivate of geraniol to which was evaluated their antioxidant activity.[1]

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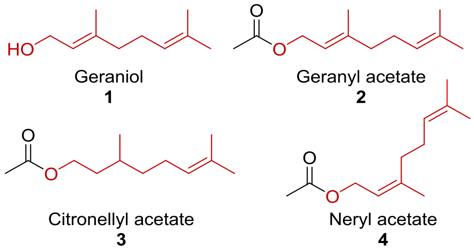
[*] Degree work

[**] Faculty of Sciences School of Chemistry. Director: Director: VLADÍMIR V. KOUZNETSOV, *Codirector:* CARLOS EDUARDO PUERTO GALVIS

INTRODUCTION

The two mainly acyclic monoterpenoids present in the essential oil (EO) of palmarosa (*Cymbopogon martinii*) are geraniol **1** (85 %) and geranyl acetate **2** (12 %).[1] Both terpenoids are of biological and commercial importance due to the antioxidant,[2] antifungal and antimicrobial[3] action of **1** and the presence of **2** in many natural fragrances (Figure 1).[4]

Figure 1. Naturally occurring monoterpenoids found in the essential oils of palmarosa (**1**, **2**), citronella (**3**), and neroli (**4**).



Among the fragrance compounds used in the food, cosmetic and pharmaceutical industries. The terpene esters of short-chain carboxylic acids like **2**, and the acetates of terpene alcohols, citronellol **3** and nerol **4**, are the most important.[5] Traditionally, these esters are obtained by chemical synthesis or extraction from natural sources,[6] where they are generated as a result of the alcohol acetyltransferase (AAT) enzymes.[7]

The esterification reaction has been already accomplished by several chemical methods, generating many drugs, pharmaceuticals, synthetic and natural products with the ester linkage, giving the incorrect impression that there are no remaining synthetic challenges in this field. When actually, there are a few methods that offer the direct esterification, especially of terpene alcohols, with functional group tolerance under mild reaction conditions.

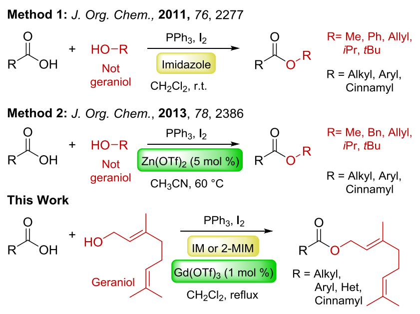
Lipases and esterases have often been used as catalysts to synthesize flavour esters by esterification of geraniol, citronellol and nerol,[8-10] but this approach has some drawbacks:

the poor structural diversity of the obtained terpene ester due to the negative effect of different carboxylic acids on the enzyme catalytic behavior, and the low yield in which the desired compound is obtained when the role of various physicochemical parameters, such as the water activity, the nature of acetyl donor, the polarity of organic solvent and the concentration of reactants, is not well controlled.[11,12]

Despite the recent efforts aimed to develop a mild reaction protocols for the chemoselective esterification of various alcohols, the substrate scope with terpene alcohols still remains as a challenge: (1) imidazole has promoted the exchange of the hydroxyl group present in the carboxylic acid by the bulky phosphonium ion, leading the phosphonium-carboxylate salt, which suffers the nucleophilic attack by the alcohol (Method 1, Scheme 1).[13] (2) the phosphonium-carboxylate salt generated, is activated by a Lewis acid in order to facilitate the intermolecular attack of the alcohol at a faster rate to produce the corresponding ester (Method 2, Scheme 1).[14] Furthermore, simple primary and secondary commercial alcohols were esterified in these two methods for high efficiency, avoiding the use of terpene alcohols (*e.g.* geraniol) from natural sources.

Therefore, development of a more practical approach, with broad substrate scope and compatible with terpene alcohols like geraniol **1** is still attractive. Herein, we report an efficient Gd-catalyzed esterification of geraniol **1**, using the commercial reagent and the EO of palmarosa, with a variety of carboxylic acids in Ph_3P/I_2/imidazole (IM) or 2-methylimidazole (2-MIM) (Scheme 1).

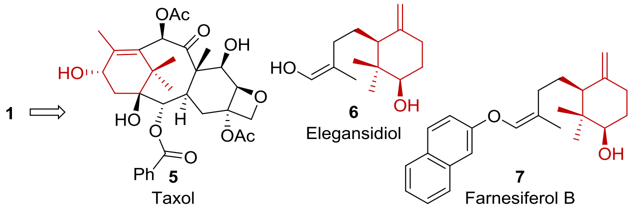
Scheme 1. Methods of esterification of different alcohols



1. METHODOLOGICAL FRAMEWORK

Developing a novel protocol for the synthesis of geranil esters from **1**, with a low catalyst loading and in good to excellent yields, was not the only challenge during our research. We notice that the inclusion of the alkyl fragment of **1** in the structure of the obtained esters could be the target and the starting point of subsequent chemical transformations of these compounds in order to prepare more structurally complex esters with functionalized cyclohexane skeletons, like the present in the key precursor of Taxol **5**, synthesized from **1** by Takahashi et. al.,[15] and the naturally occurring elegansidiol **6** and farnesiferol B **7**, both sesquiterpenoids with potent anticancer activities (Figure 2).[16]

Figure 2. Potent naturally occurring anticancer compounds with the cyclohexanol unit derived from geraniol **1**.



According to the statements described above and with the knowledge that there are no reports of an efficient method for the direct esterification of carboxylic acids with geraniol **1**, obtained from commercial and natural sources, our research was focused on: (*i*) establishing the optimal conditions for the reaction of **1** with several carboxylic acids according to the variables: solvent, reaction times, temperature, base, catalyst and loading catalyst and the yield in which the desired product is obtained. (*ii*) with the established conditions in hand, preparing a 16-membered library of new geranyl esters through the direct esterification of carboxylic acids with geraniol **1**, by the activation *in situ* of the phosphonium-carboxylate salt generated. (*iii*) obtain the EO of palmarosa and use it as a raw material for the direct esterification of some carboxylic acids under the established conditions. (*iv*) prepare a few 6,7-epoxygeranyl esters and make them react with Cp_2TiCl, a radical cyclization for the synthesis of novel (8-hydroxy-9,9-dimethyl-5-methylene cyclohexyl)methyl esters.

2. EXPERIMENTAL DESIGN

3.1 Experimental section

Infrared (FT-IR) spectra were recorded on a Lumex Infralum FT-02 spectrometer, ν_{max} in cm^{-1}. Bands are characterized according to the functional group. ^1H NMR spectra were recorded on a Bruker Avance-400 (400 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 ppm). Data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, br = broad, m = multiplet), coupling constants (Hz) and integration. ^{13}C NMR spectra were recorded on a Bruker Avance-400 (400 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from solvent resonance as the internal standard ($CDCl_3$: δ 77.00 ppm). On DEPT-135 spectra, the signals of CH_3 and CH carbons are shown as positive (+) and CH_2 carbons are shown negative (-). Quaternary carbons are not shown. A Hewlett Packard 5890a Series II Gas Chromatograph interfaced to an HP 5972 Mass Selective Detector (MSD) with an HP MS ChemStation Data system was used for MS identification at 70 eV using a 60 m capillary column coated with HP-5 [5%-phenylpoly (dimethylsiloxane)]. Accurate mass data were obtained on Micromass Q-TOF by electrospray ionisation (ESI).

Unless otherwise noted, all reactions have been carried out with distilled and dried solvents and under atmosphere pressure. All work-up and purification procedures were carried out with reagent grade solvents (purchased from Aldrich and Merck) in air. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm). Column chromatography was performed using silicagel 60 (0.063 - 0.200 mm) 70-230 mesh.

2.1 General procedure for the Gd(OTf)$_3$-catalyzed esterification of carboxylic acids with geraniol. Synthesis of geranyl esters 12a-p.

To a stirring solution of I_2 (1.5 equiv) in dry CH_2Cl_2 (35 mL) was added triphenylphosphine (1.5 mmol), giving the solution a brown-yellow color. Then, imidazole or 2-methylimidazole (3.3 mmol) was added, changing the color to light yellow. Subsequently, the carboxylic acid 11a-p (1.1 mmol) was added and the solution was stirred for 10 min at room temperature, then (1 mol %) of $Gd(OTf)_3$ was added and the stirring was continued for 30 min at 50°C. Finally, geraniol 1 (1 mmol) or the essential oil of palmarosa (183.8 mg) was added. The mixture was stirred until completely consumption of the starting material (checked by TLC, around 12-24 h). The reaction mixture was quenched with saturated sodium bicarbonate solution (10 mL, 1 M) and was extracted three times with CH_2Cl_2 (3 x 20 mL). The organic layer was separated, dried with Na_2SO_4, and concentrated to afford the crude product, which was purified by silica gel flash chromatography to yield the corresponding geranyl esters **12a-p**.

(*E*)-3,7-dimethylocta-2,6-dien-1-yl acetate (12a): Colorless oil (0.18 g, 0.94 mmol, 93%), R_f [hexane-EtOAc 15:1] = 0.7; IR (ATR, cm^{-1}): 2922 $\nu_{(CH)}$, 1738 $\nu_{(C=O)}$, 1688 $\nu_{(C=C)}$, 1229 $\nu_{(C-O)}$, 831 $\nu_{(C=C-H)}$; NMR (400 MHz, $CDCl_3$), $\delta_{(ppm)}$: 5.32 (1H, td, *J* = 7.1, 1.0 Hz, 4-*H*), 5.05 (1H, td, *J* = 6.7, 1.0 Hz, 8-*H*), 4.56 (2H, d, *J* = 7.2 Hz, O-CH_2-), 2.11–2.00 (4H, m, -CH_2-), 2.03 (3H, s, COCH_3), 1.67 (3H, s, 12-CH_3), 1.65 (3H, s, 10-CH_3), 1.57 (3H, s, 11-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$), $\delta_{(ppm)}$: 171.1, 142.3, 131.8, 123.7 (+), 118.2 (+), 61.4 (-), 39.5 (-), 26.3 (-), 25.7 (+), 21.1 (+), 17.7 (+), 16.5 (+); GC: R_t= 48.963 min, MS (EI), *m/z* (%): 196 ($M^{+\cdot}$, 37), 127 (40), 81 (41), 73 (22), 69 (100), 45 (64); HRMS (ESI+): *m/*z: calcd for $C_{12}H_{21}O_2$ ($[M+H]^+$) 197.1542, found: 197.1544; calcd for $C_{12}H_{20}NaO_2$ ($[M+Na]^+$) 219.1361, found: 219.1363.

(*E*)-3,7-dimethylocta-2,6-dien-1-yl-(*E*)-3,7-dimethylocta-2,6-dienoate (12b): Colorless oil (0.15 g, 0.49 mmol, 75%), R_f [hexane-EtOAc 20:1] = 0.65; IR (ATR, cm^{-1}): 2921 $\nu_{(CH)}$, 1671 $\nu_{(C=O)}$, 1612 $\nu_{(C=C)}$, 1246 $\nu_{(C-O)}$, 754 $\nu_{(C=C-H)}$; ^{1}H NMR (400 MHz, $CDCl_3$), $\delta_{(ppm)}$: 6.97 (1H, dd, *J* = 8.3, 1.0 Hz, 2’-H_{Ar}), 6.87 (1H, td, *J* = 7.8, 1.0 Hz, 6’-H_{Ar}), 5.46 (1H, t, *J* = 7.0 Hz, 4-*H*), 5.11–5.07 (1H, m, 8-*H*), 4.86 (2H, d, *J* = 7.1 Hz, O-CH_2-), 2.17–2.03 (8H, m, -CH_2-), 1.77 (6H, s, 10’-CH_3, 12-CH_3), 1.67 (6H, s, 8’-CH_3, 10-CH_3), 1.60 (6H, s, 9’-CH_3, 11-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$), $\delta_{(ppm)}$: 161.6, 143.4, 132.1, 123.7 (+), 117.6 (+), 62.3 (-), 39.6 (-), 26.3 (-), 25.8 (+), 17.8 (+), 16.7 (+); GC: R_t= 51.847 min, MS (EI), *m/z* (%): 304 ($M^{+\cdot}$, 28), 235 (32), 167 (44), 83 (56), 69 (100); HRMS (ESI+): *m/*z: calcd for $C_{20}H_{33}O_2$ ($[M+H]^+$) 305.2481, found: 305.2483; calcd for $C_{20}H_{32}NaO_2$ ($[M+Na]^+$) 327.2300, found: 327.2302.

(±)-(*E*)-3,7-dimethylocta-2,6-dien-1-yl-5-(1,2-dithiolan-3-yl)pentanoate (12c): Yellow oil (0.126 g, 0.353 mmol, 63%), R_f [hexane-EtOAc 15:1] = 0.5; IR (ATR cm^{-1}): 2925 $\nu_{(CH)}$, 1728 $\nu_{(C=O)}$, 1636 $\nu_{(C=C)}$, 1443 $\nu_{(C-S)}$, 1228 $\nu_{(C-O)}$, 753 $\nu_{(C-S)}$; ^{1}H NMR (400 MHz, $CDCl_3$), $\delta_{(ppm)}$: 5.35–5.31 (1H, m, 4-*H*), 5.07 (td, *J* = 6.6, 0.9 Hz, 1H, 8-*H*), 4.58 (2H, d, *J* = 7.1 Hz, -CH_2-), 3.56 (1H, dq, *J* = 8.3, 6.5 Hz, 6’-*H*), 3.21–3.07 (2H, m, 8’-*H*), 2.45 (1H, dt, *J* = 12.2, 6.6 Hz, 7a’-*H*), 2.32 (2H, t, *J* = 7.4 Hz, 2’-*H*), 2.12–2.01 (4H, m, CH_2), 1.90 (1H, dt, *J* = 19.7, 7.0 Hz, 7b’-*H*), 1.69 (3H, s, 12-CH_3), 1.67 (3H, s, 10-CH_3), 1.65–1.61 (4H, m, 3’-*H*, 4’-*H*), 1.59 (3H, s, 11-CH_3), 1.54–1.39 (2H, m, 5’-*H*); ^{13}C NMR (101 MHz, $CDCl_3$), $\delta_{(ppm)}$: 173.7, 142.4, 131.9, 123.8 (-), 118.3 (+), 61.4 (-), 56.4 (+), 40.3 (-), 39.6 (-), 38.6 (-), 34.7 (-), 34.2 (-), 28.9 (-), 26.3 (-), 25.8 (+), 24.8 (-), 17.8 (+), 16.6 (+); GC: R_t= 53.971 min, MS (EI), *m/z* (%): 342 ($M^{+\cdot}$, 31), 206 (32), 81 (44), 69 (100), 67 (28), 41 (56); HRMS (ESI+): *m/*z: calcd for $C_{18}H_{31}O_2S_2$ ($[M+H]^+$) 343.1765, found: 343.1767; calcd for $C_{18}H_{30}NaO_2S_2$ ($[M+Na]^+$) 365.1585, found: 365.1584.

(*E*)-3,7-dimethylocta-2,6-dien-1-yl-benzoate (12d): Colorless oil (0.17 g, 0.66 mmol, 85%), R_f: [hexane-EtOAc 15:1] = 0.6; IR(ATR cm^{-1}): 2923 $\nu_{(CH)}$, 1718 $\nu_{(C=O)}$, 1602 $\nu_{(C=C)}$, 1270 $\nu_{(C-O)}$, 712 $\nu_{(C=C-H)}$; ^{1}H NMR (400 MHz, $CDCl_3$), $\delta_{(ppm)}$: 8.06–8.02 (2H, m, 3’-H_{Ar}, 4’-H_{Ar}), 7.58–7.51 (1H, m, 7’-H_{Ar}), 7.42 (2H, t, *J* = 7.7 Hz, 5’-H_{Ar}, 6’-H_{Ar}), 5.49 (1H, dtd, *J* = 8.0, 6.9, 1.1 Hz, 4-*H*), 5.10–5.07 (1H, m, 8-*H*), 4.84 (2H, d, *J* = 7.1 Hz, -CH_2-), 2.09 (4H, td, *J* = 12.1, 5.7 Hz, -CH_2-), 1.76 (3H, s, 12-CH_3), 1.67 (3H, s, 10-CH_3), 1.60 (3H, s, 11-CH_3); ^{13}C NMR (101 MHz, CDCl$_3$), $\delta_{(ppm)}$: δ 166.8, 142.5, 132.9 (+), 131.9, 130.5 (+), 129.6 (+), 128.4 (+), 123.8 (+), 118.4 (+), 62.0 (-), 39.6 (-), 25.7 (+), 17.8 (+), 16.6 (+); GC: R_t= 38.290 min, MS (EI), *m/z* (%): 258 ($M^{+\cdot}$, 38), 105 (100), 69 (98), 68 (59), 77 (53), 41 (44); HRMS (ESI+): *m/*z: calcd for $C_{17}H_{23}O_2$ ([M+H]$^+$) 259.1698, found: 259.1695; calcd for $C_{17}H_{22}NaO_2$ ([M+Na]$^+$) 281.1517, found: 281.1515.

(*E*)-3,7-dimethylocta-2,6-dien-1-yl-2-chlorobenzoate (12e): Pale pink oil (0.16 g, 0.55 mmol, 82%), R_f: [hexane-EtOAc 15:1] = 0.5; IR(ATR, cm^{-1}): 2926 $\nu_{(CH)}$, 1716 $\nu_{(C=O)}$, 1610 $\nu_{(C=C)}$, 1271 $\nu_{(C-O)}$, 716 $\nu_{(C=C-H);}$ ^{1}H NMR (400 MHz, CDCl$_3$), $\delta_{(ppm)}$: 7.68 (1H, d, *J* = 7.1 Hz, 4'-H_{Ar}), 7.28 (2H, d, *J* = 4.1 Hz, 6'-H_{Ar}, 7'-H_{Ar}), 7.18–7.14 (1H, m, 5'-H_{Ar}), 5.43–5.39 (1H, m, 4-*H*), 5.14–5.11 (1H, m, 8-*H*), 4.80 (2H, d, *J* = 7.1 Hz, -CH_2-), 1.96–1.87 (4H, m, -CH_2-), 1.75 (3H, s, 12-CH_3), 1.70 (3H, s, 10-CH_3), 1.69 (3H, s, 11-CH_3); ^{13}C NMR (101 MHz, CDCl$_3$), $\delta_{(ppm)}$: 166.8, 142.5, 132.9 (+), 131.9, 130.5 (+), 129.6 (+), 128.4 (+), 128.4 (+), 123.8 (-), 118.4 (+), 62.01 (+), 39.6 (-), 26.3 (-), 25.7 (+), 17.81 (+), 16.67 (+); GC: R_t= 36.392 min, MS (EI), *m/z* (%): 292 ($M^{+\cdot}$, 34), 111 (100), 123 (59), 77 (53), 69 (98), 41 (44); HRMS (ESI+): *m/*z: calcd for $C_{17}H_{22}O_2$ ([M+H]$^+$) 293.1308, found: 292.1309; calcd for $C_{17}H_{22}NaO_2$ ([M+Na]$^+$) 315.1128, found: 315.1129.

(*E*)-3,7-dimethylocta-2,6-dien-1-yl 2-hydroxybenzoate (12f): Yellow oil (0.23 g, 0.83 mmol, 38%), R_f: [hexane-EtOAc 15:1] = 0.45; IR(ATR, cm^{-1}): 3210 $\nu_{(OH),}$ 2918 $\nu_{(CH)}$, 1671 $\nu_{(C=O)}$, 1612 $\nu_{(C=C),}$ 1210 $\nu_{(C-O)}$, 723 $\nu_{(C=C-H);}$ ^{1}H NMR (400 MHz, CDCl$_3$), $\delta_{(ppm)}$: 10.71 (1H, s, O*H*), 8.40 (1H, dd, *J* = 3.3, 1.7 Hz, 6'-H_{Ar}), 7.88 (1H, td, *J* = 7.8, 1.7 Hz, 7'-H_{Ar}), 7.66 (1H, td, *J* = 7.7, 1.1 Hz, 5'-H_{Ar}), 7.51 (1H, dd, *J* = 8.1, 1.1 Hz, 3'-H_{Ar}), 5.49–5.45 (1H, m, 4-*H*), 5.37–5.32 (1H, m, 8-*H*), 5.00 (2H, d, *J* = 7.2 Hz, -CH_2-), 2.33–2.16 (4H, m, -CH_2-), 1.98 (3H, s, 10-CH_3), 1.89 (3H, s, 12-CH_3), 1.87 (3H, s, 11-CH_3); ^{13}C NMR (101 MHz, CDCl$_3$), $\delta_{(ppm)}$: 164.5, 149.5, 142.7, 136.2 (+), 133.7 (+), 131.5, 130.6 (+), 126.4 (+), 123.7 (+), 119.4 (+), 62.1 (+), 39.3 (-), 26.1 (-), 25.6 (+), 17.6 (+), 16.2 (+); GC: R_t= 48.872 min, MS (EI), *m/z* (%): 274 ($M^{+\cdot}$, 21), 231 (67), 193 (53), 69 (100), 67 (20), 44 (28); HRMS (ESI+): *m/*z: calcd for $C_{17}H_{23}O_3$ ([M+H]$^+$) 275.3675, found: 275.3677; calcd for $C_{17}H_{22}NaO_3$ ([M+Na]$^+$) 297.3492, found: 297.3494.

(*E*)-3,7-dimethylocta-2,6-dien-1-yl 4-hydroxy-3-methoxybenzoate (12g): Colorless oil, (0.11 mg, 0.35 mmol, 40%), R_f [hexane-EtOAc 10:1]=0.2; IR (ATR, cm^{-1}): 3314 ν $_{(OH)}$, 2967 ν $_{(CH)}$, 1710 ν $_{(C=O)}$, 1634 ν $_{(C=C)}$, 1280 ν $_{(C-O)}$, 877 ν $_{(C=C-H)}$; ^1H NMR (400 MHz, $CDCl_3$), $\delta_{(ppm)}$: 7.62 (1H, dd, *J* = 8.3, 1.9 Hz, 3'-H_{Ar}), 7.53 (1H, d, *J* = 1.9 Hz, 4'-H_{Ar}), 6.90 (1H, d, *J* = 8.3 Hz, 6'-H_{Ar}), 6.50 (1H, s, O*H*), 5.42–5.37 (1H, m, 4-*H*), 5.07 (1H, ddd, *J* = 7.0, 4.0, 1.3 Hz, 8-*H*), 4.13 (2H, d, *J* = 6.9 Hz, -CH_2-), 3.92 (3H, s, 8'-CH_3), 2.08 (2H, dd, *J* = 16.1, 6.3 Hz, -CH_2-), 2.03–1.99 (2H, m, -CH_2-), 1.66-1.65 (6H, m, 10-CH_3, 12-CH_3), 1.58 (3H, s, 11-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$), $\delta_{(ppm)}$: 166.6, 150.1, 146.3 (+), 142.1 (+), 131.9, 124.2, 123.8 (+), 122.5 (+), 118.6 (+), 114.2 (+), 111.9 (+), 59.4 (-), 39.6 (-), 26.44 (-), 25.7 (+), 17.7 (+), 16.3 (+); GC: R_t= 53.971 min, MS (EI), *m/z* (%): 342 ($M^{+\cdot}$, 23), 206 (32), 81 (44), 69 (100), 67 (28), 41 (56); HRMS (ESI+): *m/*z: calcd for $C_{18}H_{25}O_4$ ($[M+H]^+$) 305.1753, found: 305.1755; calcd for $C_{18}H_{24}NaO_4$ ($[M+Na]^+$) 327.1572 found: 327.1574.

(*E*)-3,7-dimethylocta-2,6-dien-1-yl nicotinate (12h): Yellow oil (0.17 g, 0.65 mmol, 84% yield) R_f: [hexane-EtOAc 15:1] = 0.30; IR(ATR, cm^{-1}): 2920 ν $_{(CH)}$, 1719 ν $_{(C=O)}$, 1591 ν $_{(C=C)}$, 1274 ν $_{(C-O)}$, 740 ν $_{(C=C-H)}$; ^1H NMR (400 MHz, $CDCl_3$), $\delta_{(ppm)}$: 9.21 (1H, dd, *J* = 2.1, 0.7 Hz, 4'-H_{Ar}), 8.74 (1H, dd, *J* = 4.9, 1.7 Hz, 7'-H_{Ar}), 8.29–8.26 (1H, m, 3'-H_{Ar}), 7.36 (1H, ddd, *J* = 8.0, 4.9, 0.8 Hz, 5'-H_{Ar}) 5.45 (1H, td, *J* = 7.2, 1.2 Hz, 4-*H*), 5.08–5.05 (1H, m, 8-*H*), 4.85 (d, *J* = 7.1 Hz, 2H, -CH_2-), 2.14–2.03 (4H, m, -CH_2-), 1.75 (3H, s, 12-CH_3), 1.65 (3H, s, 10-CH_3), 1.58 (3H, s, 11-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$), $\delta_{(ppm)}$: 165.2, 153.2 (+), 150.9 (+), 143.0, 137.0 (+), 131.8, 126.3, 123.6 (+), 123.2, (+), 117.9 (+), 62.2 (-), 39.5 (+), 26.2 (+), 25.6 (+), 17.6 (+), 16.5 (+); GC: R_t= 22.810 min, MS (EI), *m/z* (%): 259 ($M^{+\cdot}$, 35), 124 (100), 106 (50), 78 (37), 69 (98), 41 (80); HRMS (ESI+): *m/*z: calcd for $C_{16}H_{22}NO_2$ ($[M+H]^+$) 260.1651, found: 260.1655; calcd for $C_{16}H_{21}NaNO_2$ ($[M+Na]^+$) 282.1470, found: 282.1473.

(*E*)-3,7-dimethylocta-2,6-dien-1-yl-2-phenylacetate (12i): Colorless oil (0.26 g, 0.97 mmol, 80%), R_f [hexane-EtOAc 15:1] = 0.7; IR (ATR, cm^{-1}): 2922 ν $_{(CH)}$, 1732 ν $_{(C=O)}$, 1602 ν $_{(C=C)}$, 1114 ν $_{(C-O)}$, 699 ν $_{(C=C-H)}$; ^1H NMR (400 MHz, $CDCl_3$), $\delta_{(ppm)}$: 7.35–7.23 (5H, m, 4'-H_{Ar}, 5'-H_{Ar}, 6'-H_{Ar}, 7'-H_{Ar}, 8'-H_{Ar}), 5.34 (1H, td, *J* = 7.1, 0.9 Hz, 4-*H*), 5.07 (1H, ddd, *J* =

6.9, 4.0, 1.3 Hz, 8-*H*), 4.61 (2H, d, *J* = 7.1 Hz, -C*H*$_2$-), 3.62 (2H, s, -C*H*$_2$-), 2.12–2.01 (4H, m, -C*H*$_2$-), 1.68 (6H, s, 10-C*H*$_3$, 12-C*H*$_3$), 1.60 (3H, s, 11-C*H*$_3$); ^{13}C NMR (101 MHz, CDCl$_3$), δ$_{(ppm)}$: δ 171.7, 142.4, 134.1 (+), 131.8, 129.3 (+), 128.5 (+), 127.0 (+), 123.7 (+), 118.1 (+), 61.8 (-), 41.4 (-), 39.5 (-), 26.2 (-), 25.7 (+), 17.7 (+), 16.5 (+); GC: R_t= 22.827 min, MS (EI), *m/z* (%): 272 (M$^{+\cdot}$, 30), 191 (86), 93 (32), 69 (100), 68 (40), 41 (54); HRMS (ESI+): *m/*z: calcd for $C_{18}H_{25}O_2$ ([M+H]$^+$) 273.1855, found: 273.1858; calcd for $C_{18}H_{24}NaO_2$ ([M+Na]$^+$) 295.1674, found: 295.1677.

(±)-(*E*)-3,7-dimethylocta-2,6-dien-1-yl 2-hydroxy-2-phenylacetate (12j): Yellow oil (0.19 g, 0.66 mmol, 28%), R_f: [hexane-EtOAc 15:1] = 0.5; IR(ATR, cm^{-1}): 3346 ν$_{(OH),}$ 2918 ν$_{(CH)}$, 1746 ν$_{(C=O)}$, 1669 ν$_{(C=C),}$ 1240 ν$_{(C-O)}$, 831 ν$_{(C=C-H);}$ ^{1}H NMR (400 MHz, CDCl$_3$), δ$_{(ppm)}$: 7.40–7.19 (5H, m, 3'-*H*$_{Ar}$, 4'-*H*$_{Ar}$, 5'-*H*$_{Ar}$, 6'-*H*$_{Ar}$, 7'-*H*$_{Ar}$), 5.89 (1H, s, 2'-*H*), 5.38–5.33 (1H, m, 4-*H*), 5.08–5.03 (1H, m, 8-*H*), 4.08 (2H, dd, *J* = 6.8, 0.5 Hz, -C*H*$_2$-), 2.70 (1H, s, O*H*), 2.09-1.94 (4H, m, -C*H*$_2$-), 1.64 (3H, s, 10-C*H*$_3$), 1.62 (3H, s, 12-C*H*$_3$), 1.56 (3H, s, 11-C*H*$_3$); ^{13}C NMR (101 MHz, CDCl$_3$), δ$_{(ppm)}$: 164.1, 138.8, 133.7, 131.4, 129.3 (+), 128.4 (+), 127.2 (+), 123.9 (+), 74.7 (+), 58.9 (-), 39.4 (-), 26.3 (-), 25.5 (+), 17.5 (+), 16.1 (+); GC: R_t= 42.332 min, MS (EI), *m/z* (%): 288 (M$^{+\cdot}$, 42), 271 (100), 107 (36), 77 (69), 69 (89), 41 (38); HRMS (ESI+): *m/*z: calcd for $C_{18}H_{25}O_3$ ([M+H]$^+$) 289.3945, found: 289.3948; calcd for $C_{18}H_{24}NaO_3$ ([M+Na]$^+$) 311.3762, found: 311.3765.

(*E*)-3,7-dimethylocta-2,6-dien-1-yl-3-phenylpropanoate (12k): Colorless oil, (0.141 g, 0.492 mmol, 71%), R_f [hexane-EtOAc 15:1] =0.5; IR (ATR, cm^{-1}): 2922 ν$_{(CH)}$, 1732 ν$_{(C=O)}$, 1602 ν$_{(C=C),}$ 1155 ν$_{(C-O)}$, 699 ν$_{(C=C-H)}$; ^{1}H NMR (400 MHz, CDCl$_3$), δ$_{(ppm)}$: 7.33–7.28 (2H, m, 5'-*H*$_{Ar}$, 6'-*H*$_{Ar}$), 7.24–7.19 (3H, m, 7'-*H*$_{Ar}$, 8'-*H*$_{Ar}$, 9'-*H*$_{Ar}$), 5.37–5.33 (1H, m, 4-*H*), 5.11 (1H, ddd, *J* = 6.9, 4.1, 1.3 Hz, 8-*H*), 4.63 (2H, d, *J* = 7.1 Hz, 3-*H*), 3.01–2.96 (2H, m, -C*H*$_2$-), 2.68–2.63 (2H, m, -C*H*$_2$-), 2.16–2.05 (4H, m, -C*H*$_2$-), 1.72 (6H, s, 10-C*H*$_3$, 12-C*H*$_3$), 1.63 (3H, s, 11-C*H*$_3$); ^{13}C NMR (101 MHz, CDCl$_3$), δ$_{(ppm)}$: 172.9, 142.2, 140.6 (+), 131.8, 128.5 (+), 128.3 (+), 126.2, 123.8 (+), 118.3 (+), 61.4 (-), 39.5 (-), 35.9 (-), 31.0 (-), 26.3 (-), 25.7 (+), 17.7 (+), 16.5 (+); GC: R_t= 38.897 min, MS (EI), *m/z* (%): 286 (M$^{+\cdot}$, 34), 217 (74), 91 (100), 69 (88), 67 (44); HRMS (ESI+): *m/*z: calcd for $C_{19}H_{27}O_2$ ([M+H]$^+$) 287.2011, found: 287.2013; calcd for $C_{19}H_{26}NaO_2$ ([M+Na]$^+$) 309.1830, found: 309.1833.

(*E*)-3,7-dimethylocta-2,6-dien-1-yl-3-(4-methoxyiphenyl)propanoate (12l): Colorless oil (0.137 g, 0.432 mmol, 68%), R_f [hexane-EtOAc 15:1] = 0.4; IR (ATR, cm^{-1}): 2915 $\nu_{(CH)}$, 1731 $\nu_{(C=O)}$, 1613 $\nu_{(C=C)}$, 1245 $\nu_{(C-O)}$, 825 $\nu_{(C=C-H)}$; ^{1}H NMR (400 MHz, CDCl$_3$), $\delta_{(ppm)}$: 7.14–7.10 (2H, m, 7’-H_{Ar}, 8’-H_{Ar}), 6.84–6.81 (2H, m, 5’-H_{Ar}, 6’-H_{Ar}), 5.32 (1H, ddd, *J* = 7.1, 2.4, 1.2 Hz, 4-*H*), 5.09 (1H, ddd, *J* =6.9, 4.1, 1.3 Hz, 8-*H*), 4.59 (2H, d, *J* = 7.1 Hz, -CH_2-), 3.78 (3H, s, 10’-CH_3), 2.90 (2H, t, *J* = 7.8 Hz, -CH_2-), 2.62–2.58 (2H, m, -CH_2-), 2.13–2.02 (4H, m, -CH_2-), 1.69 (6H, s, 10-CH_3, 12-CH_3), 1.61 (3H, s, 11-CH_3); ^{13}C NMR (101 MHz, CDCl$_3$), $\delta_{(ppm)}$: 173.1, 158.0 (+), 142.3, 132.7, 131.9, 129.3 (+), 123.8 (s, 8-*H*), 118.3 (+), 113.9 (+), 61.4 (-), 55.2 (+), 39.6 (-), 36.3 (-), 30.2 (-), 26.3 (-), 25.8 (+), 17.8 (+), 16.5 (+); GC: R_t= 20.89 min, MS (EI), *m/z* (%): 316 (M$^{+\cdot}$, 33), 179 (46), 137 (58), 121 (100), 93 (30), 69 (72); HRMS (ESI+): *m/*z: calcd for $C_{20}H_{29}O_3$ ([M+H]$^+$) 317.2117, found: 317.2119; calcd for $C_{20}H_{28}NaO_3$ ([M+Na]$^+$) 339.1936, found: 339.1938.

(*E*)-3,7-dimethylocta-2,6-dien-1-yl-cinamate (12m): Colorless oil (0.167 g, 0.587 mmol, 90% yield) R_f: [hexane-EtOAc 15:1] = 0.5; IR (ATR, cm^{-1}): 2926 $\nu_{(CH)}$, 1709 $\nu_{(C=O)}$, 1636 $\nu_{(C=C)}$, 1162 $\nu_{(C-O)}$, 767 $\nu_{(C=C-H);}$ ^{1}H NMR (400 MHz, CDCl$_3$), $\delta_{(ppm)}$: 7.70 (1H, d, *J* = 16.0 Hz, -C*H*-), 7.54-7.49 (2H, m, 5’-H_{Ar}, 6’-H_{Ar}), 7.41–7.35 (3H, m, 7’-H_{Ar}, 8’-H_{Ar}, 9’-H_{Ar}), 6.46 (1H, d, *J* = 16.0 Hz, -C*H*-), 5.45–5.41 (1H, m, 4-*H*), 5.12–5.08 (1H, m, 8-*H*), 4.74 (2H, d, *J* = 7.1 Hz, -CH_2-), 2.16–2.05 (4H, m, -CH_2-), 1.75 (3H, d, *J* = 1.1 Hz, 12-CH_3), 1.69 (3H, d, *J* = 1.0 Hz, 10-CH_3), 1.61 (3H, s, 11-CH_3); ^{13}C NMR (101 MHz, CDCl$_3$), $\delta_{(ppm)}$: 167.1, 144.7 (+), 142.5 (+), 134.5, 131.9, 128.9 (+), 128.1 (+), 123.8 (+), 118.3 (+), 118.2 (+), 61.5 (-), 39.6 (-), 26.3 (-), 25.8 (+), 17.8 (+), 16.6 (+); GC: R_t= 26.069 min, MS (EI), *m/z* (%): 284 (M$^{+\cdot}$, 38), 131 (100), 103 (40), 93 (52), 69 (57), 41 (32); HRMS (ESI+): *m/*z: calcd for $C_{19}H_{25}O_2$ ([M+H]$^+$) 285.1855, found: 285.1858; calcd for $C_{19}H_{24}NaO_2$ ([M+Na]$^+$) 307.1674, found: 307.1677.

(*E*)-3,7-dimethylocta-2,6-dien-1-yl (*E*)-3-(4-hydroxy-3-methoxyphenyl)acrylate (12n): Colorless oil (2.02 mg, 0.605 mmol, 10%), R_f [hexane-EtOAc 4:1] = 0.4; IR (ATR, cm^{-1}): 3347 $\nu_{(OH)}$, 2918 $\nu_{(CH)}$, 1692 $\nu_{(C=O)}$, 1631 $\nu_{(C=C)}$, 1158 $\nu_{(C-O)}$, 817 $\nu_{(C=C-H)}$; ^{1}H NMR (400 MHz, CDCl$_3$), $\delta_{(ppm)}$: 7.62 (1H, d, *J* = 15.9 Hz, -C*H*-), 7.06 (1H, dd, *J* = 8.2, 1.8 Hz, 5’-H_{Ar}), 7.02 (1H, d, J_{HH}= 1.9 Hz, 7’-H_{Ar}), 6.91 (1H, d, *J* = 8.1 Hz, 6’-H_{Ar}), 6.30 (1H, d, *J* =

15.9 Hz, -CH_2-), 5.92 (1H, s, OH), 5.42 (1H, td, *J* = 7.1, 1.2 Hz, 4-*H*), 5.09 (1H, ddd, *J* = 6.8, 4.1, 1.3 Hz, 8-*H*), 4.72 (2H, d, *J* = 7.2 Hz, -CH_2-), 3.91 (3H, s, 10’-CH_3), 2.15–2.04 (4H, m, -CH_2-), 1.74 (3H, s, 12-CH_3), 1.68 (3H, s, 10-CH_3), 1.60 (3H, s, 11-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$), $\delta_{(ppm)}$: δ 167.5, 147.9, 146.8 (+), 144.9 (-), 142.5, 132.0, 127.2, 123.8 (+), 123.2 (+), 118.4 (+), 115.6 (-), 114.8, 109.2 (+), 61.4 (-), 56.0 (+), 39.7 (-), 26.4 (-), 25.8 (+), 17.8 (+), 16.6 (+); GC: R_t= 50.875 min, MS (EI), *m/z* (%): 330 ($M^{+\cdot}$, 31), 206 (32), 149 (100), 81 (44), 69 (80), 44 (32); HRMS (ESI+): *m/*z: calcd for $C_{20}H_{27}O_4$ ([M+H]$^+$) 331.1909, found: 331.1907; calcd for $C_{20}H_{26}NaO_4$ ([M+Na]$^+$) 353.1729, found: 353.1727.

(*E*)-3,7-dimethylocta-2,6-dien-1-yl-(3,4-dimethoxy)cinnamate (12o): Colorless oil (89.2 mg, 0.25 mmol, 54%), R_f: [hexane-EtOAc 10:1] = 0.6; IR (ATR, cm^{-1}): 2967 $\nu_{(CH)}$, 1706 $\nu_{(C=O)}$, 1634 $\nu_{(C=C)}$, 1257 $\nu_{(C\text{-}O)}$, 732 $\nu_{(C=C\text{-}H)}$; ^{1}H NMR (400 MHz, $CDCl_3$), $\delta_{(ppm)}$: 7.62 (1H, d, *J* = 15.9 Hz, -CH_2-), 7.08 (1H, dd, *J* = 8.3, 1.9 Hz, 6’-H_{Ar}), 7.03 (1H, d, *J* = 1.9 Hz, 8’-H_{Ar}), 6.84 (1H, d, *J* = 8.3 Hz, 5’-H_{Ar}), 6.32 (1H, d, J_{HH}= 15.9 Hz, -CH_2-), 5.43–5.38 (m, 4-*H*), 5.08 (1H, td, *J* = 5.6, 2.9 Hz, 8-*H*), 4.71 (2H, d, *J* = 7.1 Hz, -CH_2-), 3.89 (6H, d, *J* = 2.3 Hz, 10’-CH_3, 11’-CH_3), 2.15–1.98 (4H, m, -CH_2-), 1.73 (3H, s, 12-CH_3), 1.67 (3H, s, 10-CH_3), 1.59 (s, 3H, 11-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$), $\delta_{(ppm)}$: 167.3, 151.0, 149.1, 144.6, 142.4 (+), 131.9, 127.4, 123.3 (+), 122.7 (+), 118.4 (+), 115.9 (+), 111.0 (+), 109.4, 61.4 (-), 55.9 (+), 39.6 (-), 26.3 (-), 25.7 (+), 17.7 (+), 16.6 (+); GC: R_t= 21.159 min, MS (EI), *m/z* (%): 334 ($M^{+\cdot}$, 18), 241 (70), 153 (18), 69 (100), 68 (23), 67 (22); HRMS (ESI+): *m/*z: calcd for $C_{21}H_{29}O_4$ ([M+H]$^+$) 335.2066, found: 335.2068; calcd for $C_{21}H_{28}NaO_4$ ([M+Na]$^+$) 367.1885, found: 367.1888.

(*E*)-3,7-dimethylocta-2,6-dien-1-yl-(3,4,5-trimethoxy)cinnamate (12p): Colorless oil (24.0 mg, 0.629 mmol, 47 %), R_f [hexane-EtOAc 15:1] = 0.3; IR (ATR, cm^{-1}): 2926 $\nu_{(CH)}$, 1707 $\nu_{(C=O)}$, 1636 $\nu_{(C=C)}$, 1272 $\nu_{(C\text{-}O)}$, 826 $\nu_{(C=C\text{-}H)}$; Spectroscopy NMR data for **12p** ^{1}H NMR (400 MHz, $CDCl_3$), $\delta_{(ppm)}$: 7.59 (1H, d, J_{HH}= 15.9 Hz, -CH_2-), 6.74 (2H, s, 5’-H_{Ar}, 6’-H_{Ar}), 6.35 (1H, d, J_{HH}= 15.9 Hz, -CH_2-), 5.43–5.38 (1H. m, 4-*H*), 5.10–5.06 (1H, m, 8-*H*), 4.72 (2H, d, *J* = 7.1 Hz, -CH_2-), 3.86 (m, 10’-CH_3, 11’-CH_3, 12’-CH_3), 2.14–1.99 (4H, m, -CH_2-), 1.74 (3H, s, 12-CH_3), 1.67 (3H, s, 10-CH_3), 1.59 (3H, s, 11-CH_3); ^{13}C NMR (101

MHz, $CDCl_3$), $\delta_{(ppm)}$: 167.0, 153.5, 144.7 (+), 142.6, 131.9, 117.9 (+), 105.3 (+), 61.5 (-), 56.2 (+), 39.6 (-), 26.4 (-), 25.7 (+), 16.62 (+), 16.35 (+); GC: R_t= 37.930 min, MS (EI), *m/z* (%): 374 ($M^{+\cdot}$, 25), 238 (100), 223 (54), 221 (69), 169 (49), 41 (49); HRMS (ESI+): *m/z*: calcd for $C_{22}H_{31}O_5$ ($[M+H]^+$) 375.2171, found: 375.2173; calcd for $C_{22}H_{30}NaO_5$ ($[M+Na]^+$) 397.1991, found: 397.1993.m

2.2 General procedure for the synthesis of 6,7-epoxy geranyl esters 13a-k.

A mixture of the geranyl ester **12** (0.8 mmol) and $NaHCO_3$ (0.88 mmol) in CH_2Cl_2 (15 mL) was cooled to 0°C, and m-CPBA (0.88 mmol) was added. The reaction was stirred at that temperature for 2 hours and then the mixture was allowed to reach room temperature and stirred for 30 min. TLC monitoring confirmed the end of the reaction and the reaction mixture was filtered and treated with a saturated aqueous solution of $NaHCO_3$, then extracted three times with CH_2Cl_2 (3 x 20 mL) and the organic layer was separated, dried with Na_2SO_4, and concentrated to afford the crude product, which was purified by silica gel flash chromatography to yield the corresponding 6,7-epoxy geranyl esters **13a-k**.

(*E*)-3,7-dimethylocta-2-en, 6,7-epoxy-1-yl acetate (13a): Colorless oil (46.0 mg, 0.22 mmol, 35% yield); R_f [hexane-EtOAc 15:1] = 0.4; IR (ATR, cm^{-1}): 2963 $\nu_{(CH)}$, 1735 $\nu_{(C=O)}$, 1616 $\nu_{(C=C)}$, 1230 $\nu_{(C-O)}$, 1022 ν ($_{C-O\ epox}$), 870 $\nu_{(C=C-H)}$; ^1H NMR (400 MHz, $CDCl_3$), $\delta_{(ppm)}$: 5.37-5.33 (1H, m, 4-*H*), 4.56 (2H, d, *J* = 7.1 Hz, -CH_2-), 2.67 (1H, t, *J* = 6.2 Hz, 8-*H*), 2.17 (2H, qd, *J* = 14.4, 7.2 Hz, -CH_2-), 2.02 (3H, s, 2'-CH_3), 1.69 (3H, s, 12-CH_3), 1.66–1.60 (2H, m, -CH_2-), 1.27 (3H, s, 10-CH_3), 1.23 (3H, s, 11-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$), $\delta_{(ppm)}$: 171.1, 141.3, 118.8 (+), 63.9 (+), 61.3 (-), 58.5, 36.2 (-), 27.0 (-), 24.9 (+), 21.1 (+), 18.8 (+), 16.5 (+). GC: R_t= 24.237 min, MS (EI), *m/z* (%): 212 ($M^{+\cdot}$, 53), 193 (18), 69 (100), 68 (23), 67 (22), 41 (70); HRMS (ESI+): *m/z*: calcd for $C_{12}H_{21}O_3$ ($[M+H]^+$) 213.1491, found: 213.1494; calcd for $C_{12}H_{20}NaO_3$ ($[M+Na]^+$) 253.1310, found: 253.1313.

(±)-(*E*)-3,7-dimethylocta-2-en-6,7-epoxy-1-yl-5-(1,2-dithiolan-3-yl)pentanoate (13b): Yellow oil (238.0 mg, 0.639 mmol, 30% yield); R_f [hexane-EtOAc 15:1] = 0.3; IR (ATR, cm^{-1}): 2928 $\nu_{(CH)}$, 1726 $\nu_{(C=O)}$, 1262 $\nu_{(C-O)}$, 1075 ν ($_{C-O\ epox}$), 732 $\nu_{(C=C-H)}$; ^1H NMR (400

MHz, $CDCl_3$), $\delta_{(ppm)}$: δ 5.35–5.30 (1H, m, 4-*H*), 4.59 (2H d, *J* = 7.1 Hz, -CH_2-), 3.59 (1H, m, 6’-*H*), 3.36–3.25 (2H, m, -CH_2-), 3.08–2.98 (1H m, 8-*H*), 2.37–2.30 (2H m, -CH_2-), 2.13–2.00 (4H, m, -CH_2-), 1.91–1.80 (2H, m, -CH_2-), 1.70 (3H, s, 12-CH_3), 1.68 (1H, s, 10-CH_3), 1.66–1.61 (4H, m, -CH_2-), 1.60 (1H, s, 10-CH_3), 1.49–1.40 (1H, m, 11-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$), $\delta_{(ppm)}$: δ 173.3, 142.6, 118.2 (+), 75.4 (+), 61.5 (-), 59.7, 55.3 (+), 39.6 (-), 36.7 (-), 36.3 (-), 34.0 (-), 33.9 (-), 28.2 (-), 26.4 (-), 25.8 (+), 24.8 (-), 17.8 (+), 16.6 (+); GC: R_t= 23.511 min, MS (EI), *m/z* (%): 358 ($M^{+\cdot}$, 46), 285 (100), 159 (73), 73 (69), 43 (40); HRMS (ESI+): *m/*z: calcd for $C_{18}H_{31}O_3S_2$ ($[M+H]^+$) 359.5625, found: 359.5627; calcd for $C_{18}H_{30}NaO_3S_2$ ($[M+Na]^+$) 381.5442, found: 381.5444.

(*E*)-3,7-dimethylocta-2-en-6,7-epoxy-1-yl-benzoate (13c): Colorless oil (0.106 g, 0.968 mmol, 40%), R_f: [hexane-EtOAc 15:1] = 0.3; IR (ATR, cm^{-1}): 2962 $\nu_{(CH)}$, 1715 $\nu_{(C=O)}$, 1601 $\nu_{(C=C)}$, 1268 $\nu_{(C-O)}$, 1107 $\nu_{(C-O\ epox)}$, 710 $\nu_{(C=C-H)}$ cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), $\delta_{(ppm)}$: 8.04 (2H, dt, *J* = 8.5, 1.8 Hz, 3’-H_{Ar}, 4’-H_{Ar}), 7.56–7.52 (1H, m, 7’-H_{Ar}), 7.44–7.40 (2H, m, 5’-H_{Ar}, 6’-H_{Ar}), 5.51 (1H, td, *J* = 7.0, 1.2 Hz, 4-*H*), 4.84 (2H, d, *J* = 7.0 Hz, -CH_2-), 2.71 (1H, t, *J* = 6.3 Hz, 8-*H*), 2.29–2.13 (2H, m, -CH_2-), 1.78 (3H, s, 12-CH_3), 1.73–1.65 (2H, m, -CH_2-), 1.29 (3H, s, 10-CH_3), 1.26 (3H, s, 11-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$), $\delta_{(ppm)}$: 166.7, 141.5, 132.9 (+), 130.4, 129.6 (+), 128.4 (+), 119.1 (+), 64.0 (+), 61.8 (-), 58.6, 36.3 (-), 27.1 (-), 24.9 (+), 18.8 (+), 16.6 (+); GC: R_t= 18.235 min, MS (EI), *m/z* (%): 274 ($M^{+\cdot}$, 51), 219 (36), 105 (100), 79 (42), 76 (30), 85 (24); HRMS (ESI+): *m/*z: calcd for $C_{17}H_{23}O_3$ ($[M+H]^+$) 275.1647, found: 275.1648; calcd for $C_{17}H_{22}NaO_3$ ($[M+Na]^+$) 297.1467, found: 297.1469.

(*E*)-3,7-dimethylocta-2-en-6,7-epoxy-1-yl nicotinate (13d): Red oil, 0.140 g, 0.508 mmol, 62% yield) R_f: [hexane-OEtAc 15:1] = 0.4; IR (ATR, cm^{-1}): 2961 $\nu_{(CH)}$, 1719 $\nu_{(C=O)}$, 1590 $\nu_{(C=C)}$, 1274 $\nu_{(C-O)}$, 1108 $\nu_{(C-O\ epox)}$, 871 $\nu_{(C-O\ epox\ asym.\ flex.)}$, 826 $\nu_{(C=C-H)}$; ^{1}H NMR (400 MHz, $CDCl_3$), $\delta_{(ppm)}$: 9.21 1H, (dd, *J* = 2.2, 0.8 Hz, 4’-H_{Ar}), 8.76 (1H, dd, *J* = 4.9, 1.7 Hz, 7’-H_{Ar}), 8.29 (1H, dt, *J* = 8.0, 2.0 Hz, 3’-H_{Ar}), 7.38 (1H, ddd, *J* = 8.0, 4.9, 0.9 Hz, 5’-H_{Ar}), 5.53–5.48 (1H, m, 4-*H*), 4.87 (2H, d, *J* = 7.1 Hz, -CH_2-), 2.71 (1H, t, *J* = 6.2 Hz, 8-*H*), 2.30–2.14 (2H, m, -CH_2-), 1.79 (3H, s, 12-CH_3), 1.68 (2H, td, *J* = 7.8, 6.3 Hz, -CH_2-), 1.29 (3H, s, 10-CH_3), 1.26 (3H, s, 11-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$), $\delta_{(ppm)}$: 165.4, 153.4

(+), 151.0 (+), 142.2, 137.2 (+), 126.3, 123.4 (+), 118.5 (+), 64.0 (+), 62.2 (-), 58.5, 36.3 (-), 27.1 (-), 24.9 (+), 18.8 (+), 16.7 (+); GC: R_{t}= 41.448 min, MS (EI), *m/z* (%): 275 ($\mathrm{M}^{+\cdot}$, 49), 206 (100), 124 (67), 79 (51), 78 (44), 85 (35); HRMS (ESI+): *m/*z: calcd for $C_{16}H_{22}NO_3$ ($[M+H]^+$) 276.1600, found: 275.1603; calcd for $C_{16}H_{21}NNaO_3$ ($[M+Na]^+$) 298.1419, found: 298.1417.

(*E*)-3,7-dimethylocta-2-en-6,7-epoxy-1-yl 2-chlorobenzoate (13e): Pale pink oil (98.0 mg, 0.32 mmol, 79 % yield); R_{f} [hexane-OEtAc 15:1] = 0.2; IR (ATR, cm^{-1}): 2962 $\nu_{\mathrm{(CH)}}$, 1726 $\nu_{\mathrm{(C=O)}}$, 1592 $\nu_{\mathrm{(C=C)}}$, 1246 $\nu_{\mathrm{(C\text{-}O)}}$, 748 $\nu_{\mathrm{(C=C\text{-}H)}}$; ^{1}H NMR (400 MHz, $CDCl_3$), $\delta_{\mathrm{(ppm)}}$: 7.81 (1H, dd, *J* = 7.8, 1.6 Hz, 4'-H_{Ar}), 7.42 (2H, dtd, *J* = 9.7, 7.9, 1.5 Hz, 6'-H_{Ar}, 7'-H_{Ar}), 7.30 (1H, ddd, *J* = 8.7, 5.4, *J* = 1.6 Hz, 5'-H_{Ar}), 5.53 (1H, td, *J* = 7.1, 1.2 Hz, 4-*H*), 4.87 (2H, d, *J* = 7.2 Hz, -CH_2-), 2.73 (1H, t, *J* = 6.2 Hz, 8-*H*), 2.31–2.15 (2H, m, -CH_2-), 1.80 (3H, s, 12-CH_3), 1.69 (2H, dt, *J* = 13.9, 7.0 Hz, -CH_2-), 1.30 (3H, s, 11-CH_3), 1.27 (1H, s, 10-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$), $\delta_{\mathrm{(ppm)}}$: 165.8, 142.0, 133.6 (+), 132.5, 131.4 (+), 131.0, 130.3 (+), 126.6 (+), 118.6 (+), 63.9 (+), 62.3 (-), 58.5, 36.2 (-), 27.1 (-), 24.9 (+), 18.83 (+), 16.68 (+); GC: R_{t}= 22.445 min, MS (EI), *m/z* (%): 308 ($\mathrm{M}^{+\cdot}$, 50), 209 (28), 169 (38), 111 (51), 105 (88), 85 (100); HRMS (ESI+): *m/*z: calcd for $C_{17}H_{22}ClO_3$ ($[M+H]^+$) 309.1257, found: 309.1259; calcd for $C_{17}H_{21}ClNaO_3$ ($[M+Na]^+$) 331.1077, found: 331.1079.

(*E*)-3,7-dimethylocta-2-en-6,7-epoxy-1-yl-2-phenylacetate (13f): Colorless oil (40.0 mg, 0.138 mmol, 20% yield);); R_{f} [hexane-OEtAc 15:1] = 0.3; IR (ATR, cm^{-1}): 2967 $\nu_{\mathrm{(CH)}}$, 1733 $\nu_{\mathrm{(C=O)}}$, 1594 $\nu_{\mathrm{(C=C)}}$, 1248 $\nu_{\mathrm{(C\text{-}O)}}$, 727 $\nu_{\mathrm{(C=C\text{-}H)}}$; ^{1}H NMR (400 MHz, $CDCl_3$), $\delta_{\mathrm{(ppm)}}$: 7.34–7.24 (5H, m, 4'-H_{Ar}, 5'-H_{Ar}, 6'-H_{Ar}, 7'-H_{Ar}, 8'-H_{Ar}), 5.53–5.48 (1H, m,4-*H*), 4.60 (2H, d, *J* = 7.1 Hz, -CH_2-), 3.61 (2H, s, -CH_2-), 2.70 (2H, dd, *J* = 13.7, 6.4 Hz, 8-*H*), 2.30–2.09 (2H, m,-CH_2-), 1.79 (3H, s, 12-CH_3), 1.67-1.60 (2H, m, -CH_2-), 1.29 (6H, s, 11-CH_3, 10-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$), $\delta_{\mathrm{(ppm)}}$: 171.7, 141.5, 135.0, 129.3 (+), 128.9 (+), 127.1 (+), 118.8 (+), 64.0 (+), 61.7 (-), 58.5, 41.4 (+), 36.3 (-), 27.0 (-), 24.9 (+), 18.8 (+), 16.7 (+); GC: R_{t}= 19.215 min, MS (EI), *m/z* (%): 288 ($\mathrm{M}^{+\cdot}$, 59), 208 (64), 191 (100), 116 (26), 71 (26); HRMS (ESI+): *m/*z: calcd for $C_{18}H_{25}O_3$ ($[M+H]^+$) 289.1804, found: 289.1807; calcd for $C_{18}H_{24}NaO_3$ ($[M+Na]^+$) 311.1623, found: 311.1626.

(*E*)-3,7-dimethylocta-2-en-6,7-epoxy-1-yl-3-phenylpropanoate (13g): Colorless oil (85.0 mg, 0.281 mmol, 70% yield), R_f [hexane-OEtAc 10:1] = 0.5; IR (ATR, cm^{-1}): 2960 $\nu_{(CH)}$, 1731 $\nu_{(C=O)}$, 1245 $\nu_{(C\text{-}O)}$, 1078 $\nu_{(C\text{-}O\ epox)}$, 872 $\nu_{(C=C\text{-}H)}$; ^{1}H NMR (400 MHz, CDCl$_3$), $\delta_{(ppm)}$: 7.28 (2H, t, *J* = 5.2 Hz, 5'-H_{Ar}, 6'-H_{Ar}), 7.21–7.17 (3H, m, 7'-H_{Ar}, 8'-H_{Ar}, 9'-H_{Ar}), 5.35 (1H, td, *J* = 7.1, 1.2 Hz, 4-*H*), 4.59 (2H, d, *J* = 7.1 Hz, -CH_2-), 2.95 (2H, t, *J* = 7.9 Hz, -CH_2-), 2.70 (1H, t, *J* = 6.2 Hz, 8-*H*), 2.65–2.60 (2H, m, -CH_2-), 2.26–2.10 (2H, m, -CH_2), 1.71 (3H, s, 12-CH_3), 1.65 (2H, td, *J* = 7.9, 3.7 Hz, -CH_2-), 1.30 (3H, s, 10-CH_3), 1.26 (3H, s, 11-CH_3); ^{13}C NMR (101 MHz, CDCl$_3$), $\delta_{(ppm)}$: δ 173.0, 141.3, 140.6, 128.5 (+), 128.3 (+), 118.9 (+), 64.0 (+), 61.3 (-), 58.5, 36.2 (-), 36.0 (-), 31.0 (-), 27.1 (-), 24.9 (+), 18.8 (+), 16.5 (+); GC: R_t= 19.748 min, MS (EI), *m/z* (%): 302 (M$^{+\cdot}$, 47), 225 (100), 133 (36), 91 (96), 81 (70), 71 (80); HRMS (ESI+): *m/*z: calcd for $C_{19}H_{26}O_3$ ([M+H]$^+$) 303.1960, found: 303.1963; calcd for $C_{19}H_{26}NaO_3$ ([M+Na]$^+$) 325.1780, found: 325.1783.

(*E*)-3,7-dimethylocta-2-en-6,7-epoxy-1-yl-3-(4-methoxyphenyl)propanoate (13h): Colorless oil (56.1 mg, 0.16 mmol, 81% yield); R_f (Hexane:AcOEt 10:1)=0.3 IR (ATR, cm^{-1}): 2959 $\nu_{(CH)}$, 1730 $\nu_{(C=O)}$, 1612 $\nu_{(C=C)}$, 1244 $\nu_{(C\text{-}O)}$, 1109 $\nu_{(C\text{-}O\ epox)}$, 826 $\nu_{(C=C\text{-}H)}$; ^{1}H NMR (400 MHz, CDCl$_3$), $\delta_{(ppm)}$: 7.12-7.08 (1H, m, 7'-H_{Ar}, 8'-H_{Ar}), 6.83–6.79 (1H, m, 5'-H_{Ar}, 6'-H_{Ar}), 5.37–5.32 (1H, m, 4-*H*), 4.58 (2H, d, *J* = 7.1 Hz, -CH_2-), 3.77 (3H, s, 10'-CH_3), 2.88 (2H, t, *J* = 7.8 Hz, -CH_2-), 2.69 (1H, t, *J* = 6.3 Hz, 8-*H*), 2.60–2.56 (2H, m, -CH_2-), 2.25–2.09 (2H, m, -CH_2-), 1.70 (3H, s, 12-CH$_3$), 1.68–1.62 (1H, m, -CH_2-), 1.29 (3H, s, 10-CH_3), 1.25 (3H, s, 11-CH_3); ^{13}C NMR (101 MHz, CDCl$_3$), $\delta_{(ppm)}$: 173.0, 158.0 (+), 141.3 (+), 132.6, 129.3 (+), 118.9 (+), 113.9 (+), 64.0 (+), 61.2 (-), 58.5, 55.3 (+), 36.3 (-), 36.2 (-), 30.1 (-), 27.1 (-), 24.9 (+), 18.8 (+), 16.5 (+); GC: R_t= 21.867 min, MS (EI), *m/z* (%): 332 (M$^{+\cdot}$, 44), 321 (89), 237 (100), 179 (48), 81 (48), 71 (60); HRMS (ESI+): *m/*z: calcd for $C_{20}H_{29}O_4$ ([M+H]$^+$) 333.2066, found: 333.2068; calcd for $C_{20}H_{28}NaO_4$ ([M+Na]$^+$) 355.1885, found: 355.1887.

(*E*)-3,7-dimethylocta-2-en-6,7-epoxy-1-yl-cinamate (13i): Colorless oil (0.140 g, 0.50 mmol, 40%), R_f: [hexane-OEtAc 15:1] = 0.3; IR (ATR, cm^{-1}): 2962 $\nu_{(CH)}$, 1709 $\nu_{(C=O)}$, 1636 $\nu_{(C=C)}$, 1162 $\nu_{(C\text{-}O)}$, 1101 ν ($_{C\text{-}O\ epox}$), 767 $\nu_{(C=C\text{-}H)}$; ^{1}H NMR (400 MHz, CDCl$_3$), $\delta_{(ppm)}$: 7.68 (1H, d, *J* = 16.0 Hz, 2'-*H*), 7.54–7.48 (2H, m, 5'-H_{Ar}, 6'-H_{Ar}), 7.36 (3H, dd, *J* = 6.7, 3.7 Hz, 7’-H_{Ar}, 8’-H_{Ar}, 9’-H_{Ar}), 6.43 (1H, d, *J* = 16.0 Hz, 3’-*H*), 5.45 (1H, td, *J* = 7.1, 1.3 Hz, 4-*H*), 4.72 (2H, d, *J* = 7.1 Hz, 3-*H*), 2.71 (1H, t, *J* = 6.3 Hz, 8-*H*), 2.28–2.12 (2H, m, -CH_2-), 1.76 (3H, s, 12-CH_3), 1.70–1.64 (2H, m, -CH_2-), 1.30 (3H, s, 10-CH_3), 1.26 (3H, s, 11-CH_3); ^{13}C NMR (101 MHz, CDCl$_3$), $\delta_{(ppm)}$: 167.0, 144.8 (+), 141.4, 128.9 (+), 128.1 (+), 119.0 (+), 118.1 (+), 64.0 (+), 61.4 (-), 58.5, 36.2 (-), 27.1 (-), 24.9 (+), 18.8 (+), 16.2 (+); GC: R_t= 44.189 min, MS (EI), *m/z* (%): 300 ($M^{+\cdot}$, 38), 231 (100), 103 (46), 93 (48), 69 (63), 41 (38); HRMS (ESI+): *m/z*: calcd for $C_{19}H_{25}O_3$ ($[M+H]^+$) 301.1804, found: 301.1807; calcd for $C_{19}H_{24}NaO_3$ ($[M+Na]^+$) 323.1623, found: 323.1625.

(*E*)-3,7-dimethylocta-2-en-6,7-epoxy-1-yl-(3,4-dimethoxy)cinnamate (13j): Colorless oil (18.0 mg, 0.49 mmol, 42% yield), R_f [hexane-OEtAc 10:1] = 0.3; IR (ATR, cm^{-1}): 2926 $\nu_{(CH)}$, 1707 $\nu_{(C=O)}$, 1636 $\nu_{(C=C)}$, 1272 $\nu_{(C-O)}$, 826 $\nu_{(C=C-H)}$; ^{1}H NMR (400 MHz, CDCl$_3$), $\delta_{(ppm)}$: 7.62 (1H, d, *J* = 15.1 Hz, 2’-*H*), 7.26-7.24 (2H, m, 6’-H_{Ar}, 8’-H_{Ar}), 7.06 (1H, d, *J* = 7.7 Hz, 5’-H_{Ar}), 6.62 (1H, d, *J* = 15.1 Hz, 3’-H_{Ar}), 5.43-5.36 (1H, m, 4-*H*), 4.82 (2H, d, *J* = 7.1 Hz, -CH_2-), 3.84 (3H, s, 10’-CH_3), 3.76 (3H, s, 11’-CH_3), 2.23 (1H, t, *J* = 6.0 Hz, 8-*H*), 2.06–2.01 (2H, m, -CH_2-), 1.77 (3H, s, 12-CH_3), 1.64–1.54 (2H, m, -CH_2-), 1.32 (3H, s, -CH_2-), 1.19 (3H, s, 11-CH_3); ^{13}C NMR (101 MHz, CDCl$_3$), $\delta_{(ppm)}$: 167.0, 153.4 (+), 144.8 (+), 141.6, 130.0, 118.9 (+), 117.4 (+), 105.1 (+), 64.0 (+), 61.4 (-), 58.5, 56.1 (+), 36.3 (-), 27.1 (-), 24.9 (+), 18.8 (+), 16.6 (+); GC: R_t= 23.511 min, MS (EI), *m/z* (%): 360 ($M^{+\cdot}$, 52), 241 (100), 209 (80), 167 (77), 69 (68) 43 (76); HRMS (ESI+): *m/z*: calcd for $C_{21}H_{29}O_5$ ($[M+H]^+$) 361.2015, found: 361.2018; calcd for $C_{21}H_{28}NaO_5$ ($[M+Na]^+$) 383.1834, found: 383.1836.

(*E*)-3,7-dimethylocta-2-en-6,7-epoxy-1-yl-(3,4,5-trimethoxy)cinnamate (13k): Colorless oil (0.104 g, 0.26 mmol, 42% yield), R_f [hexane-OEtAc 10:1] = 0.3; IR (ATR, cm^{-1}): 2962 $\nu_{(CH)}$, 1707 $\nu_{(C=O)}$, 1635 $\nu_{(C=C)}$, 1273 $\nu_{(C-O)}$, 1001 $\nu_{(C-O\ epox)}$, 729 $\nu_{(C=C-H)}$; ^{1}H NMR (400 MHz, CDCl$_3$), $\delta_{(ppm)}$: 7.59 (1H, d, *J* = 15.9 Hz, 2’-*H*), 6.73 (2H, s, 5’-H_{Ar}, 6’-H_{Ar}), 6.34 (1H, d, *J* = 15.9 Hz, 3’-H_{Ar}), 5.48–5.43 (1H, m, 4-*H*), 4.72 (2H, d, *J* = 7.1 Hz, 3-*H*), 3.87 (6-H, s, 10’-CH_3, 12’-CH_3) 3.86 (3H, s, 11’-CH_3), 2.72 (1H, d, *J* = 6.2 Hz, 8-*H*), 2.29–2.12 (2H, m, -CH_2-), 1.76 (3H, s, 12-CH_3), 1.71–1.64 (2H, m, -CH_2-), 1.30 (3H, s, 10-CH_3), 1.26 (3H, s, 11-CH_3); ^{13}C NMR (101 MHz, CDCl$_3$), $\delta_{(ppm)}$: 167.0, 153.4 (+), 144.8, 141.6, 130.0, 118.9 (+), 117.4 (+), 105.1 (+), 64.0 (+), 61.4 (s, 3-C), 58.5, 56.1 (+), 36.3 (-), 27.1 (-), 24.9 (+), 18.8 (+), 16.6 (+); GC: R_t= 26.167 min, MS (EI), *m/z* (%): 390 ($M^{+\cdot}$, 45), 241 (100), 109 (80), 69 (68), 67 (77), 43 (76); HRMS (ESI+): *m/*z: calcd for $C_{22}H_{31}O_6$ ($[M+H]^+$) 391.2121, found: 391.2124; calcd for $C_{22}H_{30}NaO_6$ ($[M+Na]^+$) 413.1940, found: 413.1943.

2.3 General procedure for the synthesis of (8-hydroxy-9,9-dimethyl-5-methylene cyclohexyl)methyl esters 14g-h.

A mixture of Cp_2TiCl_2 (622 mg, 2.50 mmol) and Mn dust (523 mg, 9.51 mmol) in strictly deoxygenated and anhydrous THF (6.63 mL) was stirred at room temperature until the red solution turned green. Then, a solution of **13** (200 mg, 1.19 mmol) and the triethylamine in strictly deoxygenated and anhydrous THF (2.84 mL) was added to the solution of Cp_2TiCl. After starting material consumption (checked by TLC, around 12-24 h), the reaction mixture filtered, quenched with 2 N HCl and three times with ethyl acetate (3 x 20 mL). The organic layer was separated, dried with Na_2SO_4, and concentrated to afford the crude product, which was purified by silica gel flash chromatography to yield the corresponding esters **14-15** as an inseparable mixture.

(8-hydroxy-9,9-dimethyl-5-methylene cyclohexyl)mehtyl acetate (14a): Colorless oil (154 mg, 0.725 mmol, 61% yield), Obtained as a mixture of two isomers (**14a**:**15a** = 84:16); R_f: [hexane-OEtAc 15:2] = 0.3; IR (ATR, cm^{-1}): 3429 $\nu_{(OH)}$, 2941 $\nu_{(CH)}$, 1729 $\nu_{(C=O)}$, 1612 $\nu_{(C=C)}$, 1233 $\nu_{(C-O)}$, 899 $\nu_{(C=C-H)}$; Spectroscopy NMR data for the major isomer **14a**: ^{1}H NMR (400 MHz, $CDCl_3$), $\delta_{(ppm)}$: 5.35–5.30 (1H, m, 4-*H*), 4.89 (1H, dt, *J* = 1.8, 0.9 Hz, 12-*H*a), 4.80–4.79 (1H, m, 12-*H*b), 4.54 (2H, d, *J* = 7.1 Hz, -CH_2-), 3.99 (1H, t, *J* = 6.4 Hz, 8-*H*), 2.13–2.03 (2H, m, -CH_2-), 2.00 (3H, s, 2'-CH_3), 1.68 (3H, s, CH_3-2), 1.67 (3H, s, CH_3-1), 1.65–1.59 (2H, m, -CH_2-); ^{13}C NMR (101 MHz, $CDCl_3$), $\delta_{(ppm)}$: δ 171.2, 147.4, 142.0, 118.5 (+), 111.1 (-), 75.4 (+), 61.4 (-), 35.5 (-), 32.8 (-), 21.0 (+), 17.5 (+), 16.5 (+); GC: R_t= 44.281 min, MS (EI), *m/z* (%): 212 ($M^{+\cdot}$, 12), 196 (84), 86 (70), 59 (100), 43 (40); HRMS (ESI+): *m/z*: calcd for $C_{12}H_{21}O_4$ ($[M+H]^+$) 213.1491, found: 213.1494; calcd for $C_{12}H_{20}NaO_3$ ($[M+Na]^+$) 235.1310, found: 235.1313.

(8-hydroxy-9,9-dimethyl-5-methylene cyclohexyl)methyl benzoate (14b): Pale yellow oil (176 mg, 0.681 mmol, 57 % yield), Obtained as a mixture of two isomers (**14b**:**15b** = 86:14); R_f: [hexane-OEtAc 15:2] = 0.4; IR (ATR, cm^{-1}): 3433 $\nu_{\mathrm{(OH)}}$, 2941 $\nu_{\mathrm{(CH)}}$, 1713 $\nu_{\mathrm{(C=O)}}$, 1602 $\nu_{\mathrm{(C=C)}}$, 1269 $\nu_{\mathrm{(C\text{-}O)}}$, 710 $\nu_{\mathrm{(C=C\text{-}H)}}$; Spectroscopy NMR data for the major isomer **14b**: ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$), $\delta_{\mathrm{(ppm)}}$: 8.05–8.02 (2H,m, 3'-H_{Ar}, 4'-H_{Ar}), 7.56–7.50 (m, 1H, 7'-H_{Ar}), 7.44–7.39 (2H, m, 5'-H_{Ar}, 6'-H_{Ar}), 5.52–5.47 (1H, m, 4-*H*), 4.93 (1H, dt, *J* = 1.8, 0.9 Hz, 12-*H*a), 4.84 (1H, s, -CH_2-), 4.83 (1H, d, *J* = 1.6 Hz, 12-*H*b), 4.82–4.82 (1H, m, -CH_2-), 4.05 (1H, t, *J* = 6.5 Hz, 8-*H*), 2.19–2.02 (2H, m, -CH_2-), 1.92–1.92 (1H, m, O*H*), 1.77 (3H, s, CH_3-2), 1.72 (3H, dd, *J* = 1.5, 0.9 Hz, CH_3-1), 1.70–1.65 (2H, m, -CH_2-); ^{13}C NMR (101 MHz, $\mathrm{CDCl_3}$), $\delta_{\mathrm{(ppm)}}$: 166.7, 147.3, 142.1, 132.9 (+), 130.4, 129.6 (+), 128.3 (+), 118.6 (+), 111.3 (-), 75.5 (+), 61.9 (-), 35.5 (-), 32.7 (-), 17.6 (+), 16.7 (+); GC: R_t= 44.281 min, MS (EI), *m/z* (%): 274 ($\mathrm{M}^{+\cdot}$, 14), 196 (84), 86 (70), 59 (100), 43 (40); HRMS (ESI+): *m/*z: calcd for $\mathrm{C_{17}H_{23}O_3}$ ($[\mathrm{M+H}]^+$) 275.1647, found: 275.1649; calcd for $\mathrm{C_{17}H_{22}NaO_3}$ ($[\mathrm{M+Na}]^+$) 297.1467, found: 297.1469.

(8-hydroxy-9,9-dimethyl-5-methylene cyclohexyl)methyl 2-chlorobenzoate (14c): Pale yellow oil (192 mg, 0.621 mmol, 59% yield), Obtained as a mixture of two isomers (**14c**:**15c** = 76:24); R_f: [hexane-OEtAc 15:2] = 0.4; IR (ATR, cm^{-1}): 3399 $\nu_{\mathrm{(OH)}}$, 2941 $\nu_{\mathrm{(CH)}}$, 1714 $\nu_{\mathrm{(C=O)}}$, 1592 $\nu_{\mathrm{(C=C)}}$, 1247 $\nu_{\mathrm{(C\text{-}O)}}$, 1119 $\nu_{\mathrm{(C\text{-}O)}}$, 721 $\nu_{\mathrm{(C=C\text{-}H)}}$; Spectroscopy NMR data for the major isomer **14c**: ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$), $\delta_{\mathrm{(ppm)}}$: 7.79 (1H, dd, *J* = 7.7, 1.7 Hz, 4'-H_{Ar}), 7.42–7.37 (2H, m, 6'-H_{Ar}, 7'-H_{Ar}), 7.31–7.27 (1H, m, 5'-H_{Ar}), 5.51–5.47 (1H, m, 4-*H*), 4.93–4.92 (1H, m, 12-*H*a), 4.84 (3H, m, 12-*H*b, -CH_2-), 4.04 (1H, t, *J* = 6.4 Hz, 8-*H*), 2.18–2.02 (2H, m, -CH_2-), 1.83 (1H, s, O*H*), 1.76 (3H, s, CH_3-1), 1.71 (3H, s, CH_3-2), 1.66 (2H, ddd, *J* = 9.2, 5.8, 3.0 Hz, -CH_2-); ^{13}C NMR (101 MHz, $\mathrm{CDCl_3}$), $\delta_{\mathrm{(ppm)}}$: δ 165.8, 147.3, 142.7, 132.5 (+), 131.4 (+), 131.0, 126.6, 118.2 (+), 111.3 (-), 75.4 (+), 62.4 (-), 35.5 (-), 32.7 (-), 17.6 (+), 16.7 (+); GC: R_t= 42.382 min, MS (EI), *m/z* (%): 308 ($\mathrm{M}^{+\cdot}$, 21), 256 (100), 105 (32), 135 (27), 77 (84), 66 (30); HRMS (ESI+): *m/*z: calcd for

$C_{17}H_{22}ClO_3$ ($[M+H]^+$) 309.1257, found: 309.1259; calcd for $C_{17}H_{22}ClNaO_3$ ($[M+Na]^+$) 331.1077, found: 331.1079.

(8-hydroxy-9,9-dimethyl-5-methylene cyclohexyl)methyl nicotinate (14d): Pale orange oil (162 mg, 0.586 mmol, 62% yield), R_f: [hexane-OEtAc 15:3] = 0.3; IR (ATR, cm^{-1}): 3375 $\nu_{(OH)}$, 2941 $\nu_{(CH)}$, 1720 $\nu_{(C=O)}$, 1592 $\nu_{(C=C)}$, 1278 $\nu_{(C-O)}$, 741 $\nu_{(C=C-H)}$; ^{1}H NMR (400 MHz, $CDCl_3$), $\delta_{(ppm)}$: 9.20 (1H, dd, *J* = 2.1, 0.7 Hz, 4'-H_{Ar}), 8.75 (1H, dd, *J* = 4.9, 1.7 Hz, 7'-H_{Ar}), 8.28 (1H, dt, *J* = 8.0, 2.0 Hz, 3'-H_{Ar}), 7.38 (1H, ddd, *J* = 8.0, 4.9, 0.9 Hz, 5'-H_{Ar}), 5.51–5.46 (1H, m, 4-*H*), 4.93 (1H, dt, *J* = 1.7, 0.8 Hz, 12-*H*a), 4.86 (2H, d, *J* = 7.2 Hz, -CH_2-), 4.84-4.82 (1H, m, 12-*H*b), 4.04 (1H, t, *J* = 6.4 Hz, 8-*H*), 2.16–2.06 (2H, m, -CH_2-), 1.91 (1H, s, O*H*), 1.77 (3H, s, CH_3-2), 1.72 (3H, s, CH_3-1), 1.69–1.64 (2H, m, -CH_2-); ^{13}C NMR (101 MHz, $CDCl_3$), $\delta_{(ppm)}$: 165.4, 153.3 (+), 150.9 (+), 147.4, 142.9, 137.2 (+), 126.4, 123.4 (+), 118.1 (+), 111.3 (-), 75.4 (+), 62.3 (-), 35.5 (-), 32.8 (-), 17.6 (+), 16.7 (+); GC: R_t= 43.239 min, MS (EI), *m/z* (%): 275 ($M^{+\cdot}$, 19), 217 (100), 189 (48), 136 (61), 122 (20), 78 (86); HRMS (ESI+): *m/*z: calcd for $C_{16}H_{22}NO_3$ ($[M+H]^+$) 276.1600, found: 276.1603; calcd for $C_{16}H_{22}NNaO_3$ ($[M+Na]^+$) 298.1419, found: 298.1417.

(8-hydroxy-9,9-dimethyl-5-methylene cyclohexyl)methyl 3-phenylpropanoate (14e): Yellow oil (197 mg, 0.653 mmol, 55% yield), Obtained as a mixture of two isomers (**14e**:**15e** = 80:20); R_f: [hexane-OEtAc 15:2] = 0.4; IR (ATR, cm^{-1}): 3436 $\nu_{(OH)}$, 2920 $\nu_{(CH)}$, 1726 $\nu_{(C=O)}$, 1159 $\nu_{(C-O)}$, 1076 $\nu_{(C-O)}$, 731 $\nu_{(C=C-H)}$; Spectroscopy NMR data for the major isomer **14e**: ^{1}H NMR (400 MHz, $CDCl_3$), $\delta_{(ppm)}$: 7.30–7.26 (2H, m, 5'-H_{Ar}, 6'-H_{Ar}), 7.19 (3H, dt, *J* = 4.0, 2.8 Hz, 7'-H_{Ar}, 8'-H_{Ar}, 9'-H_{Ar}), 5.34 (1H, td, *J* = 7.1, 1.3 Hz, 4-*H*), 4.95–4.94 (1H, m, 12-*H*a), 4.86–4.85 (1H, m, 12-*H*b), 4.59 (2H, d, *J* = 7.0 Hz, -CH_2-), 4.04 (1H, t, *J* = 6.5 Hz, 8-*H*), 2.97–2.92 (2H, m, 3'-*H*), 2.65–2.61 (2H, m, 2'-*H*), 2.13–2.03 (2H, m, -CH_2-), 1.73 (3H, s, CH_3-2), 1.70 (3H, s, CH_3-1), 1.69–1.64 (2H, m, -CH_2-), 1.58 (1H, s, O*H*); ^{13}C NMR (101 MHz, $CDCl_3$), $\delta_{(ppm)}$: 172.9, 147.3, 142.0, 140.5, 128.50 (+), 128.3 (+), 118.5 (+), 111.2 (-), 75.5 (+), 61.3 (-), 35.9 (-), 35.4 (-), 32.7 (-), 30.9 (-), 17.6 (+), 16.5 (+); GC: R_t= 36.198 min, MS (EI), *m/z* (%): 302 ($M^{+\cdot}$, 11), 284 (100), 163 (41), 105 (80), 77 (32);

HRMS (ESI+): *m/*z: calcd for $C_{19}H_{27}O_3$ ($[M+H]^+$) 303.1960, found: 303.1963; calcd for $C_{19}H_{26}NaO_3$ ($[M+Na]^+$) 325.1780, found: 325.1783.

(8-hydroxy-9,9-dimethyl-5-methylene cyclohexyl)methyl 3-(4-methoxyphenyl)propanoate (14f): Yellow oil (184 mg, 0.552 mmol, 54% yield), Obtained as a mixture of two isomers (**14f**:**15f** = 67:23); *R*f: [hexane-OEtAc 15:2] = 0.3; IR (ATR, cm^{-1}): 3434 $\nu_{(OH)}$, 2942 $\nu_{(CH)}$, 1713 $\nu_{(C=O)}$, 1269 $\nu_{(C-O)}$, 1111 $\nu_{(C-O)}$, 710 $\nu_{(C=C-H)}$; Spectroscopy NMR data for the major isomer **14e**: ^{1}H NMR (400 MHz, $CDCl_3$), $\delta_{(ppm)}$: 7.36-7.32 (2H, m, 5'-*H*Ar, 6'-*H*Ar), 7.25 (2H, dt, *J* = 4.1, 2.7 Hz, 7'-*H*Ar, 8'-*H*Ar), 5.39 (1H, td, *J* = 7.1, 1.3 Hz, 4-*H*), 5.00–4.99 (1H, m, 12-*H*a), 4.91–4.90 (1H, m, 12-*H*b), 4.64 (2H, d, *J* = 7.0 Hz, -C*H*2-), 4.10 (1H, t, *J* = 6.5 Hz, 8-*H*), 3.02–2.98 (2H, m, -C*H*2-), 2.70–2.66 (2H, m, -C*H*2-), 2.18–2.08 (2H, m, -C*H*2-), 1.78 (3H, s, C*H*3-2), 1.75 (3H, s, C*H*3-1), 1.73–1.69 (2H, m, -C*H*2-), 1.64 (1H, s, O*H*).; ^{13}C NMR (101 MHz, $CDCl_3$), $\delta_{(ppm)}$: δ 173.4, 147.7, 142.4, 140.9, 128.7 (+), 126.6 (+), 118.9 (+), 111.7 (-), 75.9 (+), 61.8 (-), 55.3 (+) 36.3 (-), 35.8 (-), 33.1 (-), 31.4 (-), 18.0 (+), 16.9 (+); GC: R_t= 38.732 min, MS (EI), *m/z* (%): 332 ($M^{+\cdot}$, 17), 315 (100), 246 (28); 193 (68), 135 (88); HRMS (ESI+): *m/*z: calcd for $C_{20}H_{29}O_4$ ($[M+H]^+$) 333.4475, found: 333.4477; calcd for $C_{29}H_{29}NaO_4$ ($[M+Na]^+$) 355.4292, found: 355.4295.

(8-hydroxy-9,9-dimethyl-5-methylene cyclohexyl)methyl cinnamate (14g): Yellow oil (182 mg, 0.605 mmol, 51% yield), Obtained as a mixture of three isomers (**14g**:**15g**:**17a** = 56:4:39); *R*f: [hexane-OEtAc 15:2] = 0.4; IR (ATR, cm^{-1}): 3437 $\nu_{(OH)}$, 2941 $\nu_{(CH)}$, 1708 $\nu_{(C=O)}$, 1636 $\nu_{(C=C)}$, 1164 $\nu_{(C-O)}$, 1071 $\nu_{(C-O)}$, 704 $\nu_{(C=C-H)}$; Spectroscopy NMR data for the major isomer **14g**: ^{1}H NMR (400 MHz, $CDCl_3$), $\delta_{(ppm)}$: 7.69 (1H, d, *J* = 16.0 Hz, 2'-*H*), 7.51 (2H, dt, *J* = 4.7, 3.0 Hz, 5'-*H*Ar, 6'-*H*Ar), 7.38–7.36 (3H, m, 7'-*H*Ar, 8'-*H*Ar, 9'-*H*Ar), 6.44 (1H, d, *J* = 16.0 Hz, 3'-*H*), 5.47–5.43 (1H, m, 4-*H*), 4.95–4.93 (1H, m, 12-*H*a), 4.85–4.84 (1H, m, 12-*H*b), 4.72 (2H, d, *J* = 7.1 Hz, -C*H*2-), 4.05 (1H, t, *J* = 6.7 Hz, 8-*H*), 2.16–2.04 (2H, m, -C*H*2-), 1.82 (1H, s, O*H*), 1.75 (3H, s, C*H*3-2) 1.73 (3H, s, C*H*3-1), 1.70–1.63 (2H, m, -C*H*2-); ^{13}C

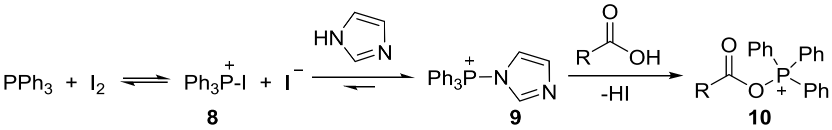
NMR (101 MHz, $CDCl_3$), $\delta_{(ppm)}$: 167.1, 147.4 (+), 142.2, 140.6, 134.4, 128.9 (+), 128.1 (+), 118.6 (+), 118.1 (-), 111.3 (-), 75.5 (+), 61.5 (-), 35.5 (-), 32.8 (-), 17.6 (+), 16.6 (+).; GC: R_t= 41.120 min, MS (EI), *m/z* (%): 300 ($M^{+\cdot}$, 13), 282 (100), 214 (44), 161 (70), 86 (23), 68 (59); HRMS (ESI+): *m/*z: calcd for $C_{19}H_{25}O_3$ ($[M+H]^+$) 301.1804, found: 301.1807; calcd for $C_{19}H_{25}NaO_3$ ($[M+Na]^+$) 323.1623, found: 323.1626.

(8-hydroxy-9,9-dimethyl-5-methylene cyclohexyl)methyl 3,4,5-trimethoxycinnamate (14h): Yellow oil (207 mg, 0.530 mmol, 45% yield), Obtained as a mixture of three isomers (**14h**:**15g**:**17b** = 47:15:38); R_f: [hexane-OEtAc 15:2] = 0.4; IR (ATR, cm^{-1}): 3381 $\nu_{(OH)}$, 2940 $\nu_{(CH)}$, 1707 $\nu_{(C=O)}$, 1636 $\nu_{(C=C)}$, 1243 $\nu_{(C-O)}$, 1001 $\nu_{(C-O)}$, 751 $\nu_{(C=C-H)}$; Spectroscopy NMR data for the major isomer **14h**: ^{1}H NMR (400 MHz, $CDCl_3$), $\delta_{(ppm)}$: 7.59 (2H, d, *J* = 15.9 Hz, 2'-*H*), 6.74 (2H, s, 5'-H_{Ar}, 6'-H_{Ar}), 6.35 (1H, d, *J* = 15.9 Hz, 3'-*H*), 5.47–5.42 (1H, m, 4-*H*), 5.29 (9H, s, 10'-CH_3, 11'-CH_3, 12'-CH_3), 4.94 (1H, dt, *J* = 1.7, 0.8 Hz, 12-*H*a), 4.84 (1H, dd, *J* = 3.0, 1.5 Hz, 12-*H*b), 4.71 (2H, d, *J* = 7.1 Hz, -CH_2-), 4.08–4.00 (1H, m, 8-*H*), 2.23–2.00 (2H, m, -CH_2-), 1.75 (3H, s, CH_3-2), 1.72 (3H, s, CH_3-1), 1.68–1.61 (2H, m, -CH_2-); ^{13}C NMR (101 MHz, $CDCl_3$), $\delta_{(ppm)}$: 167.1, 153.4, 147.4 (+), 144.8 (+), 142.1, 130.0, 118.6 (+), 117.4 (+), 111.3 (-), 105.1 (+), 75.5 (+), 61.5 (-), 56.2 (+), 35.6 (-), 32.8 (-), 17.6 (+), 16.6 (+). GC: R_t= 40.173 min, MS (EI), *m/z* (%): 390 ($M^{+\cdot}$, 13), 373 (100), 273 (41), 251 (79), 193 (61), 106 (33); HRMS (ESI+): *m/*z: calcd for $C_{22}H_{31}O_6$ ($[M+H]^+$) 391.2121, found: 391.2124; calcd for $C_{22}H_{30}NaO_6$ ($[M+Na]^+$) 413.1940, found: 413.1943.

3. RESULTS AND DISCUSSION

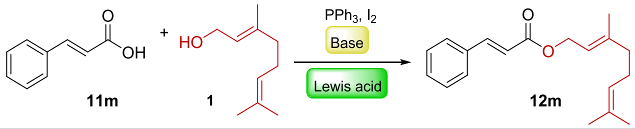
In 2011, Robles *et. al*.[13] described the utilization of phosphine, I_2 and imidazole (conditions for the Garegg-Samuelsson reaction)[17] for the esterification of various carboxylic acids with mainly methanol via formation of a phosphonium-carboxylate salt intermediate **10**. The important role of the imidazole could be explained when this base shift the equilibrium to the Ph_3P-imidazole specie **9**, from the iodotriphenylphosphonium cation **8**, and transfer the phosphonium group to the carboxylic acid, activating the carbonyl function of **10** and promoting the attack of the alcohol (Scheme 2).

Scheme 2. Formation of a phosphonium-carboxylate salt specie **10**



In accordance with this hypothesis, we initially performed the reaction between the cinnamic acid **11m** and geraniol **1** under these conditions. However, after 24 hours the reaction did not result in any detectable amount of the desired ester **12m**, not even at room temperature or 50 °C. (Table 1, entries 1 and 2).

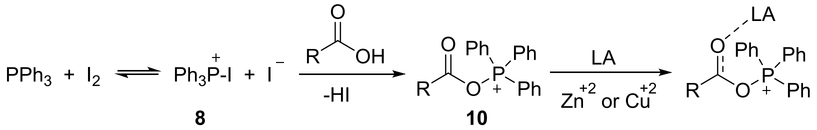
Table 1. Esterification of cinnamic acid **11m** with geraniol **1**. Screening of bases, Lewis acids and solvent systems.[a]



Entry	Base	Lewis acid (mol %)	Solvent	Yield (%)[b]
1	IM	-	CH_2Cl_2	N.R.[c]
2	IM	-	CH_2Cl_2	N.R.
3	-	$Cu(OTf)_2$ (10)	CH_3CN	N.R.
4	IM	$Sc(OTf)_3$ (10)	CH_2Cl_2	38
5	IM	$Yb(OTf)_3$ (10)	CH_2Cl_2	45
6	IM	$Dy(OTf)_3$ (10)	CH_2Cl_2	47
7	IM	$In(OTf)_3$ (10)	CH_2Cl_2	28
8	IM	$Eu(OTf)_3$ (10)	CH_2Cl_2	30
9	IM	$La(OTf)_3$ (10)	CH_2Cl_2	30
10	IM	$Cu(OTf)_2$ (10)	CH_2Cl_2	82
11	IM	$Gd(OTf)_3$ (10)	CH_2Cl_2	90
12	-	$Gd(OTf)_3$ (10)	CH_2Cl_2	N.R.
13	IM	$Gd(OTf)_3$ (10)	CH_2Cl_2	22[c]
14	IM	$Gd(OTf)_3$ (5)	CH_2Cl_2	90
15	**IM**	**$Gd(OTf)_3$ (1)**	**CH_2Cl_2**	**90**
16	2-MIM	$Gd(OTf)_3$ (1)	CH_2Cl_2	87
17	Py	$Gd(OTf)_3$ (1)	CH_2Cl_2	74
18	Pyr	$Gd(OTf)_3$ (1)	CH_2Cl_2	N.R.
19	Pyrr	$Gd(OTf)_3$ (1)	CH_2Cl_2	< 5
20	IM	$Gd(OTf)_3$ (1)	PEG-400	N.R.
21	IM	$Gd(OTf)_3$ (1)	DMSO	N.R.
22	IM	$Gd(OTf)_3$ (1)	CH_3CN	N.R.

[a] Reaction performed on a 1 mmol scale using I_2 (1.5 equiv), PPh_3 (1.5 equiv), base (3.3 equiv), **11m** (1.1 equiv), Lewis acid (1-10 mol%) and **1** (1 equiv) in the respective solvent (35 mL) for 12-24 h at 50 °C. [b] Isolated yield. [c] Reaction performed at room temperature. IM: imidazole, 2-MIM: 2-methylimidazole, Py: pyridine, Pyr: pyrimidine, Pyrr: pyrrolidine.

In 2013, Manna *et. al.*[14] reported the *in situ* activation of the phosphonium-carboxylate salt intermediate **10** by only Zn-based catalysts, without the use of imidazole as a base, for the esterification of carboxylic acids with simple alcohols. The Lewis acid (LA) activation, through the coordination with the specie **10**, appears to be necessary to enhance the electrophilicity of carbonyl function and facilitate the attack of the alcohol (Scheme 3).



Scheme 3 Activation of the phosphonium-carboxylate salt specie **10** by a Lewis acid

Nevertheless, this activation was not enough to promote the condensation of cinnamic acid **11m** and geraniol **1**, when Cu(OTf)$_2$ was used, in acetonitrile at 60 °C (Table 1, entry 3).

With the same model reaction, we hypothesized that a complete and efficient protocol for the esterification of less reactive alcohols like geraniol **1** should include: *i*) a base, to favor the formation of the phosphonium-carboxylate salt intermediate **10**, according to the described in Scheme 2, and to regulate the pH of the reaction system due to the liberation of hydrogen iodide (HI) because it is well documented the degradation of **1** under acidic conditions;[18] and *ii*) a Lewis acid, to activate the phosphonium-carboxylate salt intermediate **10**, according to the described in Scheme 3, enhancing the reactivity of this specie. Therefore, to investigate the feasibility of the two statements depicted above, we encouraged our efforts to accomplish the esterification of cinnamic acid **11m** with **1** under PPh$_3$/I$_2$ system, in CH$_2$Cl$_2$ as a solvent at 50 °C, and using imidazole (IM) as a base, with a catalytic amount (10 mol %) of a series of triflates as Lewis acid (Table 1, entries 4-9). In this way, we obtained the desired ester in low to moderate yields (28-45 %) with most of the triflates tested, being In(OTf)$_3$ the lowest with 28 % (Table 1, entry 7) and Yb(OTf)$_3$ the higher with 45 %.

Having checked the viability of this process under the proposed conditions, we found that contrary to the Manne's report, Cu(OTf)$_2$ resulted to be an excellent catalyst for this reaction with geraniol **1** and the ester **12m** was obtained in 82 % yield in CH$_2$Cl$_2$ at 50 °C (Table 1, entry 10). The best results were obtained with Gd(OTf)$_3$, affording the title compound in 90 % yield (Table 1, entry 11). However, even with the better activating agent, this reaction did not work in the absence of IM as a base (Table 1, entry 12), suggesting that under this reaction conditions the presence of **1** could affect the integrity of **10** or shift the equilibrium to the iodotriphenylphosphonium cation **8** (Scheme 3). The temperature plays an important role also, although the activation of the specie **10** by the

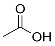
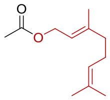
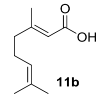
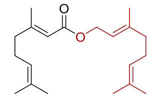
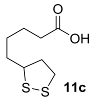
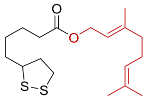
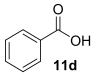
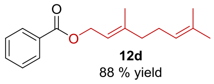
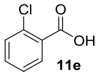
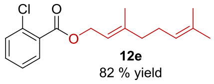
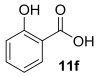
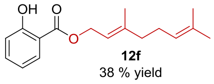
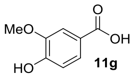
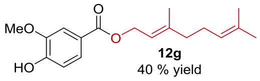
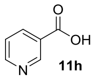
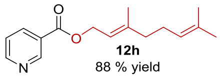
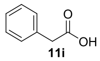
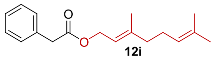
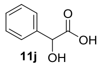
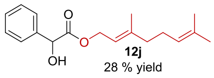
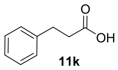
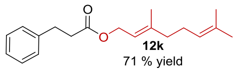
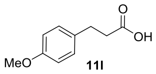
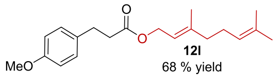
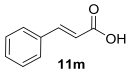
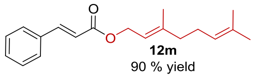
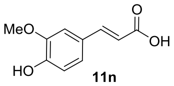
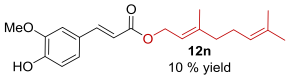
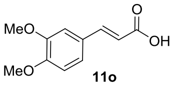
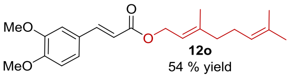
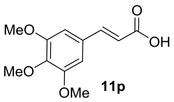
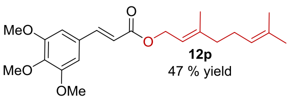
Gd(OTf)$_3$ is enough to carry out the reaction at room temperature, the yield in which the ester was obtained (22 %) was lower than the experiments carried at 50 °C (Table 1, entry 13).

Encouraged by these promising results, we decided to optimize the reaction conditions studying the effect of reducing the catalyst loading to 5 and 1 mol % (Table 1, entries 14 and 15, respectively). The best result was obtained with 1 mol % of Gd(OTf)$_3$ catalyst with CH$_2$Cl$_2$ as solvent and IM as a base at 50 °C. Interestingly, when 2-methylimidazole (2-MIM) was tested as a base, the yield in which the ester was afforded was 87 % (Table 1, entry 16), indicating that the reaction was not affected for the steric hindrance of the base. Unfortunately, when other heterocyclic bases such as pyridine (py), pyrimidine (pyr) and pyrrolidine (pyrr) (Table 1, entries 17-19) were also tested, only pyridine gave the ester in good yield. Finally, a set of solvents were studied but the desired product was not obtained either (Table 1, entries 20-22). This fact suggests that CH$_2$Cl$_2$ could act as an efficient barrier to protect the intermediates **8-10** from oxygen and moisture than other hydrophilic solvents.

Having the optimized reaction conditions in hand, the versatility of our protocol was broadened to other acids with different functional groups (aliphatic, aromatic, heterocyclic and α,β-unsaturated carboxylic acids) to establish the scope and limitations of this process. Thus, the esterification of geraniol **1** with carboxylic acids **11a-p** proceeded smoothly and afforded the corresponding esters **12a-p** with great efficiency. The results are given in Table 2.

Table 2. Synthesis of geranil esters under the optimized reaction conditions^a

Entry	Carboxylic acid	Time (h)	Product^b

1	 **11a**	2	 **12a** 93 % yield
2	 **11b**	2.5	 **12b** 75 % yield
3	 **11c**	4	 **12c** 63 % yield
4	 **11d**	3	 **12d** 88 % yield
5	 **11e**	3	 **12e** 82 % yield
6	 **11f**	6	 **12f** 38 % yield
7	 **11g**	6	 **12g** 40 % yield
8	 **11h**	3	 **12h** 88 % yield
9	 **11i**	3	 **12i** 80% yield
10	 **11j**	3	 **12j** 28 % yield
11	 **11k**	3	 **12k** 71 % yield
12	 **11l**	3	 **12l** 68 % yield
13	 **11m**	3	 **12m** 90 % yield
14	 **11n**	6	 **12n** 10 % yield
15	 **11o**	24	 **12o** 54 % yield
16	 **11p**	3	 **12p** 47 % yield

[a] Reaction performed on a 1 mmol scale using I_2 (1.5 equiv), PPh_3 (1.5 equiv), IM or 2-MIM (3.3 equiv), **11a-p** (1.1 equiv), $Gd(OTf)_3$ (1 mol%) and **1** (1 equiv) in CH_2Cl_2 (35 mL) at 50 °C. [b] Isolated yield after SiO_2 column chromatography.

The simplest acid, acetic acid **11a**, gave the higher yield for the respective geranyl acetate **12a**, result comparable with the previous reports that use enzymes (Table 2, entry 1).[8-10] While other aliphatic carboxylic acids with internal and external double bonds, the geranic acid **12b** itself, and with labile and sensitive groups like the disulfide bond of (±)-α-lipoic acid **12c**, gave moderate to good yields without the observation of any by products (Table 2, entries 2 and 3). Aromatic rings bearing different electron withdrawing and electron donating groups all furnished the target ester **12d-h** as well (40-88% yield). The steric hindrance of the substituent groups at the *ortho* position did not affect the reaction and afforded the esters **12e** and **12f** with a higher yield (Table 2, entries 4−8). It is noteworthy that nicotinic acid (Vitamin B_3) **11h** also gave the corresponding ester **12h** in 88% yield (Table 2, entry 8), proving the utility of our protocol for the preparation of heterocyclic esters derived from niacin, which are uncommon and less studied. Benzyl and dihydrocinnamic acids could also be transformed into the ester scaffold in quite moderate yields, 50-71 % (Table 2, entries 9-12).

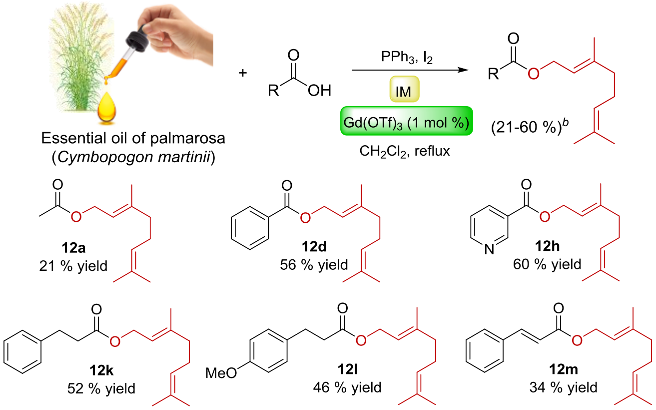
Finally, other cinnamic acids also underwent the esterification reaction to afford the respective cinnamyl esters **12m-p**, and except for **12m**, the yields were somewhat very low, 10-47 % (Table 2, entries 14-16). Nevertheless, even if this esterification method for the synthesis of geranyl esters seemed original and encouraging, it had a drawback. When the solubility of the carboxylic acids in dichloromethane is partial or minimum, the respective esters were obtained in low yields, as shown in Table 2 (entries **7**, **9**, **10**, **14** and **15**). Also, other structurally diverse carboxylic acids were tested but their insolubility in dichloromethane did not yield the desired compound, even in other solvents different from those described in Table 1 (results are not shown).

Prioritizing on the use of raw materials as precursors in organic synthesis and green methodologies, we have already published novel results on this topic in which the essential oil of anise and bud clove were used as starting materials for the synthesis of *N*-heterocyclic compounds.[19]

For this study, we had the opportunity to work with the EO of palmarosa acquire by hydrodistillation from the dried leaves and stems of *Cymbopogon martinii*. With this conventional warming procedure the EO of palmarosa was obtained in 0.4 ± 0.2% yield.

The gas chromatography with a selective mass detector of this EO indicated the presence of two principal components: geraniol **1** (83.9 %) and geranyl acetate **12a** (9.2 %).[20] This EO of palmarosa, enriched with geraniol **1**, was used to perform the esterification reaction, under the established conditions in Table 1, with some selected carboxylic acids in order to examine the scope of our protocol when this raw material is employed (Table 3).

Table 3. Synthesis of geranil esters using the EO of palmarosa enriched with **1** as raw material[a]



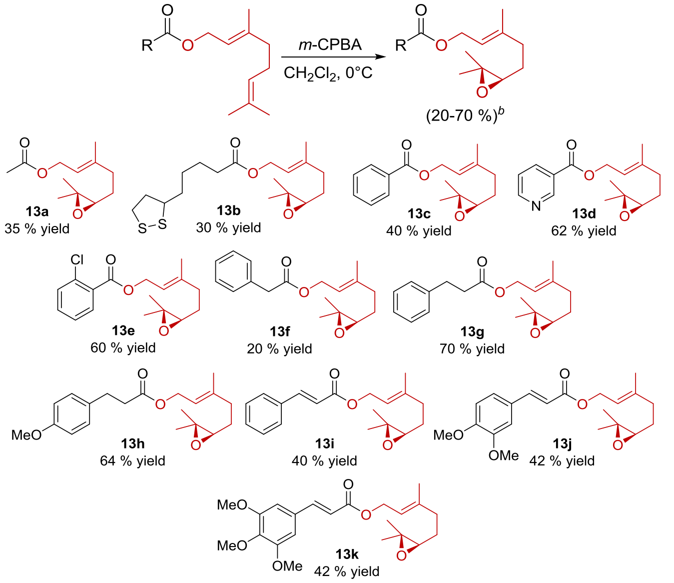
[a] Reaction performed on a 1 mmol scale using I_2 (1.5 equiv), PPh_3 (1.5 equiv), IM or 2-MIM (3.3 equiv), **11** (1.1 equiv), $Gd(OTf)_3$ (1 mol%) and 183.8 mg of the EO of palmarosa in CH_2Cl_2 (35 mL) at 50 °C. [b] Yields calculated based on the 83.9 % of **1** present in the EO and after the purification by SiO_2 column chromatography.

To our delight, these reactions proceeded smoothly and gave in moderate yields and with excellent selectivity the desired esters under the adopted reaction conditions, without detecting any by product. Although the yields of the esterification reaction, using the EO of palmarosa, did not lead to comparable results when **1** (commercial reagent) was employed, perhaps due to the fact that the EO of palmarosa is a complex mixture of compounds where other reactive terpenes are present (e.g. cinalool, cis- and trans- β-ocimene, trans-β-caryophyllene). It is still attractive the use of substrates obtained from natural sources, combined with a good synthetic protocol, to contribute to the developing of a modern and sustainable organic chemistry that focus on the synthesis of novel compounds with a complex molecular architecture.

Encourage for the efficient protocol developed for the synthesis of novel geranyl esters and to demonstrate the scope and importance of including the alkyl fragment of geraniol **1** into the structure of the esters **12a-m**, we focus our attention in explore the reactivity of this fragment toward the synthesis of the 8-hydroxy-9,9-dimethyl-5-methylenecyclohexyl core through the Ti(III)-mediated regiocontrolled radical cyclization of the respective 6,7-monoepoxy derivatives.

The next step of this approach involved the Prilezhaev reaction[21] of some selected esters **12**. Treatment the esters with *m*-chloroperbenzoic acid (*m*-CPBA) afforded, chemoselectively, the 6,7-epoxy geranyl esters **13a-k** in moderate yields (Table 4). The relative configuration of **13a-k** was assigned by analogy with similar epoxyesters, reported by Fernández-Mateos *et. al.*[22] elsewhere, and from the configuration of the products **14**, to be explored further below.

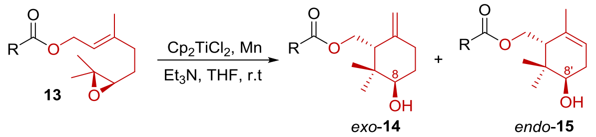
Table 4. Synthesis of 6,7-epoxy geranyl esters **13a-k** under Prilezhaev reaction conditions[a]

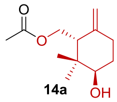
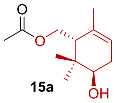
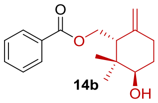
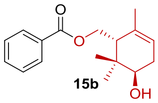
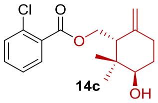
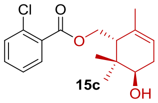
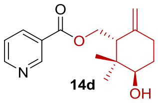
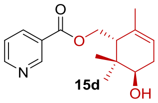
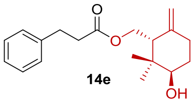
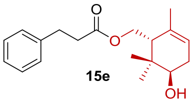
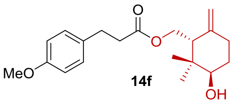
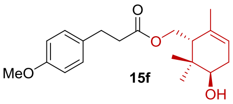


[a] Reaction performed on a 0.8 mmol scale using **12** (0.8 mmol), $NaHCO_3$ (0.88 mmol) and *m*-CPBA (0.88 mmol) in CH_2Cl_2 (15 mL) at 0 °C. [b] Isolated yield after SiO_2 column chromatography.

Finally, the last objective of our study was to address the synthesis of the (8-hydroxy-9,9-dimethyl-5-methylene cyclohexyl)methyl esters and the Ti(III)-promoted radical cyclization of the epoxy derivatives **13** seemed to be an appropriate method to access to the seven-membered ring present in some natural and bioactive products (**5-7**).[23] Our approach was based on the Cp_2TiCl-catalyzed reductive C-C bond formation, leading to a secondary cyclohexyl alcohol after the regioselective homolytic opening of the 6,7-epoxy function in **13**. To date, a few computational methods have suggested the determining role played by Cp_2TiCl in driving the stereochemical outcome of the reaction.[24] In this way, and under these reaction conditions, a selected series of epoxides **13** were allowed to react with Cp_2TiCl_2 (2.1 equiv), Mn dust (8 equiv) and Et_3N (1.7 equiv) in degassed THF (0.1 M) at room temperature for 24 hours (Table 5).

Table 5. Ti(III)-promoted the radical cyclization of the 6,7-epoxy geranyl esters **13**[a]

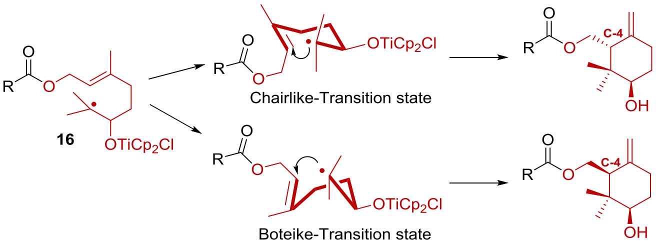


Entry	Yield (**14**+**15**)[b]	*exo*-**14**	*endo*-**15**
1	61	 **14a**	 **15a**
		Ratio[c]: 84:16	
2	57	 **14b**	 **15b**
		Ratio[c]: 86:14	
3	59	 **14c**	 **15c**
		Ratio[c]: 76:24	
4	62	 **14d**	 **15d**
		Ratio[c] 100:0	
5	55	 **14e**	 **15e**
		Ratio[c]: 80:20	
6	54	 **14f**	 **15f**
		Ratio[c] 67:23	

[a] Reaction performed on a 1 mmol scale using Cp_2TiCl_2 (2.1 equiv), Mn dust (8 equiv), the ester **13** (1 mmol) and Et_3N (1.7 equiv) in strictly deoxygenated THF (0.1 M, 9.44 mL) at room temperature for 24 hours. [b] Isolated yield after SiO_2 column chromatography. [c] Ratio of **14** and **15** in the obtained product mixture determined by ^1H-NMR spectroscopy (H-8/H-8').

During this assays made in our laboratory, the titanocene(III)-catalyzed cyclization of the 6,7-epoxy esters **13** gave the cyclohexanols **14** and **15** as an inseparable mixture in moderate yields. The alcohols *exo*-**14a-f**, with *exocycle* double bonds, were always obtained as the major products derived from the 6-endo-trig cyclization pathway, which also generated the compounds with the *endocycle* double bonds *endo*-**15a-f** but in relative minor percentage. The preference for the formation of the *exo* double bond over the *endo* double bond was described by Cuerva *et al.*[25] in 2001, when Cp_2TiCl was used for the first time to promote the cyclization of epoxides derived from commercially available geranyl acetate. However, it is worth noting that in the case of the 6,7-epoxy geranyl ester **13d**, derived from nicotic acid **11h**, the (8-hydroxy-9,9- dimethyl-5-methylene cyclohexyl)methyl ester **14d** was obtained exclusively without any trace of the *endo*-**15d** isomer, as determined by ^{1}H NMR. Some studies have shown that the double bond formation arises from a mixed disproportionation reaction between the organic radicals and Cp_2TiCl, promoted by the presence of an oxidant agent in the reaction media.[26] We suggest that the pyridine ring itself could act as an oxidant group in this case, under the employed reaction conditions, controlling the final oxidative process that allows the exclusive formation of the cyclohexanol core with the *exo* double bond.

The structure of the (8-hydroxy-9,9-dimethyl-5-methylene cyclohexyl)methyl esters **14a-f** was elucidated through ^{1}H, ^{13}C and 2D NMR spectroscopic data as illustrated for **14d**. The ^{1}H-NMR spectrum of **14d** showed a general group of characteristic signals for the aromatic protons present in the pyridine ring and the protons of the cyclohexanol moiety. This six-member ring assumes a chair conformation due to the present of one carbon atom with sp^2 hybridization in which both *exo* double bond and the hydroxyl group are in equatorial positions. The reaction mechanism could involve two possible pathways: one in which during the transition state, the β-titanoxy radical **16** formed when one electron is transferred from the titanocene(III) complex to the epoxide function, is able to approach to the 2,3-double bond by a *chairlike* conformation, establishing the *R* configuration of the tetrahedral stereocenter at C-4. In the second, the β-titanoxy radical **16** approach to the 2,3-double bond by a *botelike* conformation will establish the *S* configuration of the tetrahedral stereocenter at C-4 (Scheme 4).



Scheme 4. Possible *chairlike* and *botelike* conformation during the cyclization of the *β*-titanoxy radical

The chair conformation has been reported as the most stable form of alkylidenecyclohexanes when alkyl substituents are present at position 2, where they adopt an axial conformation due to the strong repulsive interaction between alkyl groups in equatorial form.[28] In this way, this group, the ester function in **16**, must be force to adopt an axial orientation, during the *chairlike*-transition state (Scheme 4), to allow and reach the proposed geometry, explaining satisfactorily the complete *R* configuration of the stereocenter at C-4.

The HMBC and NOESY experiments were relevant to prove the relative stereochemistry of C-4 and C-8 (Figure 3).

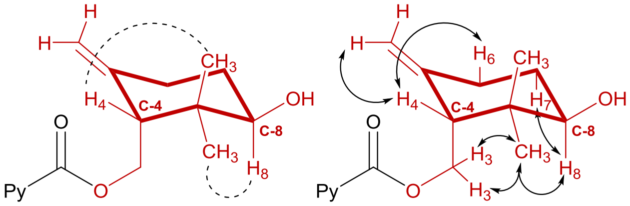
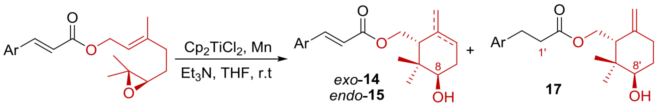


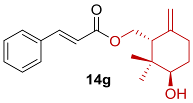
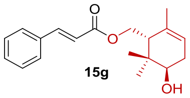
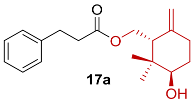
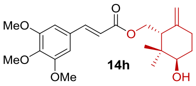
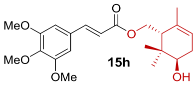
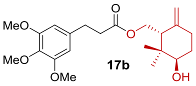
Figure 3. Selected HMBC (----) and NOESY (↔) correlations.

Having defined the stereochemistry of C-4, the HMBC correlation of the two methyl groups (axial and equatorial) of C-9 will prove the orientation of protons H-4 and H-8. Thus, proton H-4 is correlated just with Me-equatorial, while H-8 is correlated just with Me-axial. On the other hand, the NOESY correlations of H-4 equatorial with one of the protons of the exo double bond, with the proton H-6 equatorial and with the protons of the Me-equatorial, confirm the previous assignation of the stereochemistry of C-4. Moreover, the NOESY correlations for H-8 axial with the axial groups H-7 and the protons of the Me, suggest the stereochemistry of C-8. This last statement was confirmed by the key NOESY correlation of the methylene protons H-3 with only the protons of the Me-axial. Finally, because no NOESY correlation between H-4 and H-8 was found, indicating that they are not in the same plane, the final relative configuration of the six-membered ring of **14d** was confirmed and also, by the position of the hydroxyl group in the C-8, the configuration of the respective 6,7-epoxy geranyl esters **13a-k** could be well defined too.

Last, when a couple of 6,7-epoxy geranyl esters derived from cinnamic acids **13i** and **13k** were subjected to the reaction conditions employed for the radical cyclization promoted by Ti(III). We found that in addition to the respective *exo*-**14g-h** and *endo*-**15g-h** products, a third compound was detected in which the sensitive *α*,*β*-unsaturated bond of the cinnamic acid was reduced by the action of the Ti(III) (Table 6).

Table 6. Ti(III)-promoted the radical cyclization and "one-pot" reduction of 6,7-epoxy geranyl esters derived from cinnamic acids **13i** and **13k**[a]



Entry	*exo*-**14**	*endo*-**15**	**17**
1	 **14g**	 **15g**	 **17a**
	Yield:[b] 51 %; Ratio[c] (56:5:39)		
2	 **14h**	 **15h**	 **17b**
	Yield:[b] 45 %; Ratio[c] (47:15:38)		

[a] Reaction performed on a 1 mmol scale using Cp_2TiCl_2 (2.1 equiv), Mn dust (8 equiv), the ester **13** (1 mmol) and Et_3N (1.7 equiv) in strictly deoxygenated THF (0.1 M, 9.44 mL) at room temperature for 24 hours. [b] Isolated yield after SiO_2 column chromatography. [c] Ratio of **14**, **15** and **17** in the obtained product mixture determined by ^{1}H-NMR spectroscopy (H-8/H-8'/H-1').

Although, Cp_2TiCl has been used widely in different type of reductions,[23] some authors have suggested that the formation of products **17a-b** could be the result of an efficient hydrogen atom transfer (HAT) process from a titanocene(III) aquocomplex, formed by the presence of adventitious water, to the *α*,*β*-unsaturated bond of the cinnamic acid.[29] However, due that the reaction is performed under strictly anhydrous reaction conditions, other should be the hydrogen donor.

Bearing in mind that the formation of the *β*-titanoxy radical **16** releases equal amounts of HCl, the cyclization reaction needs to carried out in the presence of a triethylamine. Thus, the neutralization of the acid will produce triethylamine hydrochloride ($Et_3N \cdot HCl$), specie that proved to be a good hydrogen donor for reducing conjugate systems where the Cp_2TiCl could easily interact with, like the *α,β*-unsaturated carbonyl derivatives (**13**, **14** and **15**).[30]

4. CONCLUSIONS

We have achieved a new strategy for the straightforward esterification of geraniol with different carboxylic acids, with the added value of having used the essential oil of palmarosa (*Cymbopogon martinii*) as a readily available raw material, complementing the alternative previously reported esterification methods of simple alcohols. Based on the Garegg-Samuelsson reaction conditions (triphenylphosphine and I_2), we have found the efficiency of gadolinium ion to assist the activation of the phosphonium-carboxylate salt intermediate **10** and promote the selective esterification of less reactive geraniol **1** under mild reaction conditions without affecting his integrity.

In addition, an expedient two-step procedure for the stereoselective synthesis of (8-hydroxy-9,9-dimethyl-5-methylene cyclohexyl)methyl esters **14a-h**, based on the titanocene(III) 6-endo-trig radical cyclization, is reported. We found that this reaction elapses via a *chairlike*-transition state pattern, which allows the relative configuration of the C-4 and C-8 stereocenters of the six-membered ring of **14**. Although the yields and the selectivity (*endo*/*exo* double bond) in some cases are low, an improvement in reaction conditions might be seen as desirable for general organic chemistry, taking as a start point the results shown in this research.

This protocol represents one of the few examples in which novel esters have been prepared, from a renewed method, to study their final functionalization for the preparation of several natural products with the ester linkage and sesquiterpenoids with different skeletons containing cyclohexane rings like elegansidiol **6**. Our current interest is focused to gain a comprehensive understanding of the overall reactions and to widen the scope of these innovative processes for testing them in the synthesis of bioactive natural products.

*S Supporting Information

Characterization data of selected compounds by COSY, HSQC and HMBC experiments, extraction and characterization of the essential oil of palmarosa (*Cymbopogon martinii*) and copies of ^{1}H NMR, ^{13}C NMR, DEPT-135, COSY, HSQC and HMBC charts of all synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

Author information

Corresponding Author

*E-mail: *vkuznechnik@gmail.com*; *kouznet@uis.edu.co*.

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