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Mediterranean Journal of Chemistry **2017**, 6(4), 98-107

Experimental and theoretical analysis of the reactivity and regioselectivity in esterification reactions of diterpenes (totaradiol, totaratriol, hinikione and totarolone)

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Abstract: Six esters have been synthesized in the acetylation, benzoylation and Baeyer-Villiger oxidation of starting materials totaradiol 1, totaratriol 2, hinikione 7 and totarolone 8. A complete theoretical study of the reaction has been carried out including highly regioselectivity induction experiments and using density functional methods B3LYP/6-31G(d). The analysis of the nucleophilic Parr functions P^-_k and the electrostatic potential in diterpenes 1 and 2 offered an explanation of the regioselectivity found in these reactions and in Baeyer-Villiger reaction we use transition state theory and the electrostatic potential to understand the high regioselectevity observed, we found that the regioselectivity is kinetically and thermodynamically favorable and the electronic density is located in the multi-substituted carbon.

Keywords: Regioselectivity, esterification, diterpene, Parr function, DFT B3LYP/6-31G(d).

Introduction

Tetraclinis articulata, is a resinous tree of the Cupressaceae family originating from North Africa and south Europe, different parts of T. articulata are used as remedies in folk medicine due to supposed antidiarrhoeal, antipyretic and antirheumatic properties[1], studies show that the essential oil of Tetraclinis articulata (Vahl) exhibits a very important activity such as: Antimicrobial activity[2,3], Antibacterial activity[4,5], antifungal activity[6,7], antioxidant, anti-inflammatory activities[8,9] and good inhibitory effect on corrosion of carbon steel in acidic media[10], the diterpenes and their derivatives were evaluated to have biological activity like anticancer properties [11]. To improve the chemical and pharmacological properties of some diterpenes **1** (8-isopropyl-1,1,4a,9,10,10a-octahydro-phenanthrene-2,7-diol), **2** (8-isopropyl-1,1,4a,9,10,10a-octahydro-phenanthrene-2,3,7-triol), **7** (6-Hydroxy-7-isopropyl-1,1,4a-trimethyl-3,4,4a,9,10,10a-hexahydro-1H-phenanthren-2-one) and **8** (7-Hydroxy-8-isopropyl-1,1,4a-trimethyl-3,4,4a,9,10,10a-hexahydro-1H-phenanthren-2-one) illustrated in Scheme 1, the starting materials of Tetraclinis articulata species, we have realized the acetylation and benzoylation of alcohols. These reactions were an important and routinely utilized transformation in organic chemistry [12-14], and to prepare lactones we use the Baeyer-Villiger (B.V) oxidation is the oxidative cleavage of a carbon-carbon bond adjacent to a carbonyl, which converts ketones to esters and cyclic ketones to lactones. The B.V oxidation can be carried out either with peroxyacids, such as m-CPBA (meta-chloroperbenzoic acid). On the other hand, in the last years the density functional theory (DFT) has been successful in explaining the reactivity and regioselectivity of the reactions. In this sense, the regioselectivity of esterification reactions for diterpenes derivatives has been studied using Parr functions and the electrostatic potential. The experimentally study has been rationalized within the framework of conceptual DFT-based descriptors [15], trying to obtain some information about the factors affecting the reactivity and selectivity throughout esterification reaction of diterpenes 1, 2, 7 and 8.

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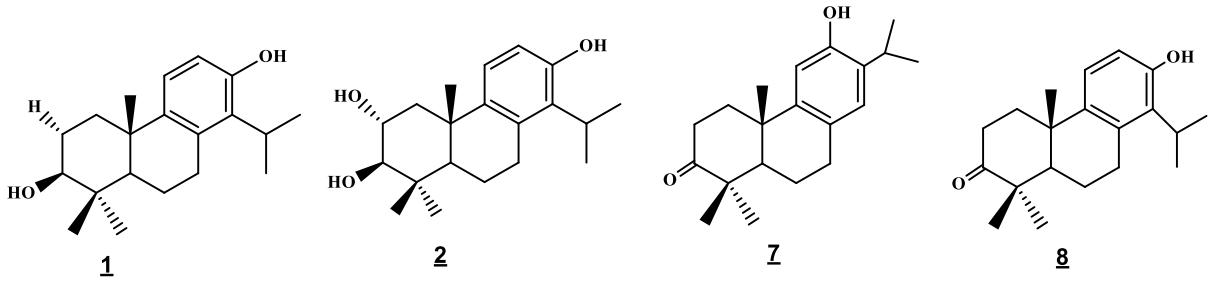
DOI: http://dx.doi.org/10.13171/mjc64/01704101226-zeroual

Received February 17, 2017
Accepted March 7, 2017
Published April 10, 2017



Scheme 1: Structures of diterpenes **1**, **2**, **7** and **8**

Computational methods

DFT computations were carried out using the B3LYP functional [16], together with the standard 6-31G* basis set**.** The optimizations have been realized using the Berny analytical gradient optimization method [17]. All computations have been carried out with the Gaussian 09 suite of programs [18]. The global electrophilicity index ω [19], was given by the following expression, $\omega = (\mu^2/2\eta)$, in terms of the electronic chemical potential μ and the chemical hardness η. Both quantities could be approached in terms of the one-electron energies of the frontier molecular orbital HOMO and LUMO, ε_H and ε_L, , as $\mu \approx (\varepsilon_H + \varepsilon_L)/2$ and $\eta \approx (\varepsilon_L - \varepsilon_H)$, respectively [20]. The empirical (relative) nucleophilicity index N [21], based on the HOMO energies obtained within the Kohn–Sham scheme [22], and defined as $N = E_{HOMO}(Nu) - E_{HOMO}(TCE)$. The nucleophilicity was referred to tetracyanoethylene (TCE). This choice allowed us to handle conveniently a nucleophilicity scale of positive values. Electrophylic P^+_k and nucleophilic P^-_k Parr functions [23-27], were obtained through the analysis of the Mulliken atomic spin density (ASD) of the radical anion and radial cation of the reagents. The local electrophilicity indices were evaluated using the following expressions: $N_k = N.P^-_k$ [28]. The stationary points were characterised by frequency computations in order to verify that TSs have one and only one imaginary frequency. Intrinsic reaction coordinate (IRC) [29] pathways were traced to verify the connectivity between minima and associated TSs. Solvent effects of dichloromethane were taken into account through single point energy calculations using the polarisable continuum model (PCM) developed by Tomasi's group in the framework of the self consistent reaction field [30]

The nuclei and electrons of a molecule create an electrostatic potential V(r) at any point r in the surrounding space:

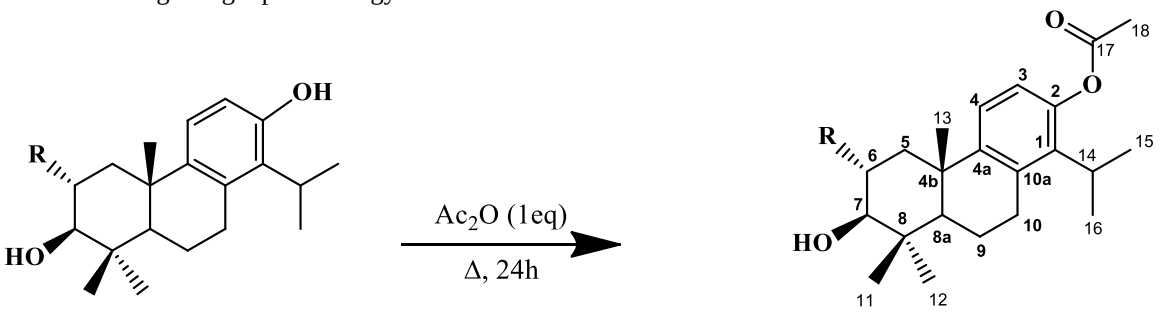
$$V(r) = \sum_A \frac{Z_A}{|R_A - r|} - \int \frac{\rho(r')dr'}{|r' - r|} \qquad (1)$$

Where Z_A is the charge on nucleus A and $\rho(r)$ is the molecule's electronic density. The sign of V(r) in any region is determined by whether the positive contribution of the nuclei or the negative one of the electrons is dominant there. Regions where $V(r) > 0$ can be expected to be attracted favorably, at least initially, to negative portions of other molecules, while $V(r) < 0$ predicts attractive interactions with positive portions.

Results and Discussion

Experimental results

In order to prepare new esters of diterpene derivatives, we were interested to the reactivity of diterpenic di- and triol hemisynthesized from Tetraclinis articulata species using acetylation and benzoylation condensation. Thus, treatment with equimolecular quantity of compounds **1**, **2** and acetic anhydride, yielded respectively, after heating at reflux during 24h, to products **3** and **4** with high regioselectivity. (Scheme 2)

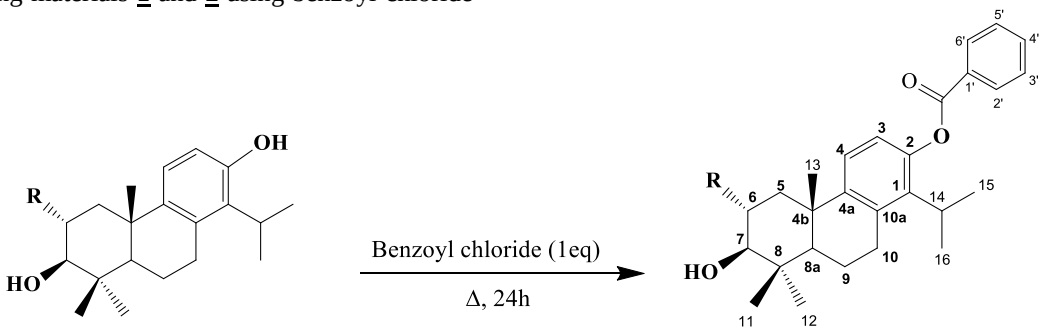


1 R = H
2 R = OH

3 R = H
4 R = OH

Scheme 2: Regioselectivity of acetylation reactions

The products **5** and **6** were obtained, by treating the starting materials **1** and **2** using benzoyl-chloride under the same condition as before (Scheme 3).



1 R = H
2 R = OH

5 R = H
6 R = OH

Scheme 3. Regioselectivity of benzoylation reactions

The entire newly prepared product **3**, **4**, **5** and **6** were fully characterized from their spectral data (NMR). Thus, ^{1}H NMR spectrum showed more especially four peaks at 2.08, 3.12, 6.66 and 6.81 ppm corresponding to H-16, H-14, H-3 and H-4 resonance for product **3** whereas the same signals are observed at 2.10, 3.15, 6.68 and 6.83 ppm for component **4**. Compounds **5** and **6** were characterized more especially in its ^{1}H and ^{13}C NMR by new signals after condensation on benzoyl chloride. The same signals are observed as before using its ^{1}H NMR, but also too new peaks have been shown corresponding to aromatic protons. The ^{13}C NMR spectrum revealed particular signals at 168.0 and 73.6 ppm assigned respectively to CO and OH groups for product **5**. However, the same signals were observed at 168.1, 74.1 and 72.6 ppm for compound **6**.

General procedure for the thermal reactions
Acetylation

A solution of diterpene **1** or **2** (80 mg, 0.265 mmol, 0.251 mmol) in acetic anhydride (20 ml) and pyridine (20 ml) was heated under reflux for 24 h. After cooling, the mixture was acidified with 1N HCl solution then extracted with ether (3 × 20 ml). The organic layer was washed with water, dried on anhydrous Na_2SO_4 and then evaporated under reduced pressure. The obtained residue was chromatographed on silica gel column using hexane and ethyl acetate (97/3) as eluent, in 92% yield.

Benzoylation

A solution of diterpene **1** or **2** (80 mg, 0.265 mmol, 0.251 mmol) in benzoyl chloride (3 ml) and pyridine (20 ml) was refluxed for 24 hours. After cooling, the mixture was acidified with HCl (1N solution), and then extracted with ether (3×20 ml). The organic layer was washed with water, dried on anhydrous Na_2SO_4 and then evaporated under reduced pressure. The obtained residue was chromatographed on a silica gel column using hexane and ethyl acetate (97/3) as eluent, to give benzoic acid 7-hydroxy-1-isopropyl-4b,8,8-trimethyl-4b,5,6,7,8,8a,9,10-octahydro-phenanthren-2-yl ester **5** and benzoic acid 6,7-dihydroxy-1-isopropyl-4b,8,8-trimethyl-4b,5,6,7,8,8a,9,10-octahydro-phenanthren-2-yl ester **6** in 92 % yield.

Baeyer-Villiger

The oxidation of (hinikione **7**, totarolone **8**), isolated from the Tetraclinis articulata plant, hinikione **7** and totarolone **8** were dissolved in chloroform (50 ml), 1ml of trifluoroacetic, and 1 equivalent of meta-chloroperbenzoic acid (m-CPBA) were added. The mixture was stirred at room temperature for 3 days and yielded compound (**L 1, L3**) in 85% yield.

2-Hydroxy-3-isopropyl-7,7,11a-trimethyl-5,6a,7,10,11,11a-hexahydro-6H-8-oxa-cyclohepta[a] naphthalene-9-one **L 1**.
Colorless oil;

^{1}H NMR (CDCl3, 300 MHz) 1.45 (3H, s, H-7), 1.42 (3H, s, H-11a), 1.56 (2H, t, J=8Hz, H-13), 2.80 (2H, t, J=8Hz, H-5), (1H, sept, *J* = 6.9 Hz, H-isopr), 6.40 (1H, s, H-1), 6.71 (1H, s, H-4);
^{13}C NMR (CDCl3, 300 MHz) 111.9 (C-1), 151.9 (C-2), 132.6 (C-3), 127.1 (C-4), 128.4 (C-4a), 30.5 (C-5), 25.8 (C-6), 73.1 (C-7),172.0 (C-9), 127.1 (C-10), 35.9 (C-11), 24.9 (C-12), 24.8 (C-13), 24.7 (C-14), 24.8 (C-15), 25.3 (C-16), 25.2 (C-17).

3-Hydroxy-4-isopropyl-7,7,11a-trimethyl-5,6a,7,10,11,11a-hexahydro-6H-8-oxa-cyclohepta[a]naphthalen-9-one **L 3**.
Colorless oil;

^{1}H NMR (CDCl3, 300 MHz) 1.29 (3H, d, J=8Hz, H-16), 1.3 (3H, d, J=8Hz, H-17), 1.44 (3H, s, H-12), 1.46 (3H, s, H-13), (1H, sept, *J* = 7 Hz, H-isopr), 4.96 (1, s,OH), 6.36 (1H, d,J=6.9 Hz, H-2), 6.98 (1H,d,J=6.9Hz, H-2);

^{13}C NMR (CDCl3, 300 MHz) 123.9 (C-1), 121.3 (C-2), 152.7 (C-3), 136.5 (C-4), 135.8 (C-4a), 325.6 (C-5), 26.9 (C-6), 61.8 (6a), 73.4 (C-7),173.1 (C-9), 28.9 (C-10), 36.1 (C-11), 34.5 (11a) 25.1 (C-12),

25.2 (C-13), 25.1 (C-14), 18.5 (C-15), 25.1 (C-16), 25.0 (C-17).

Acetic acid 7-hydroxy-1-isopropyl-4b,8,8-trimethyl-4b,5,6,7,8,8a,9,10-octahydro-phenanthren-2-yl ester ***3***.
Colorless oil;

^{1}H NMR (CDCl3, 300 MHz) 1.11 (3H, s, H-11), 1.13 (3H, s, H-12), 1.44 (3H, s, H-13), 2.08 (3H, s, H-18), 1.30 (3H, d, J = 7.0 Hz, H-15), 1.31 (3H, d, J = 7.0 Hz, H-16), 3.28 (1H, sept, *J* = 6.9 Hz, H-14), 6.66 (1H, d, J = 8.5 Hz, H-3), 6.81 (1H, d, J = 8.5 Hz, H-4);

^{13}C NMR (CDCl3, 300 MHz) 142.1 (C-1), 147.9 (C-2), 118.6 (C-3), 124.1 (C-4), 141.1 (C-4a), 29.5 (C-4b), 32.7 (C-5), 24.9 (C-6), 79.6 (C-7), 34.2 (C-8), 53.9 (C-8a), 29.9 (C-9), 24.6 (C-10), 19.1 (C-11), 19.7 (C-12), 25.5 (C-13), 15.8 (C-14), 24.7 (C-15), 24.82 (C-16), 168.2 (C-17), 17.1 (C-18).

Acetic acid 6,7-dihydroxy-1-isopropyl-4b,8,8-trimethyl-4b,5,6,7,8,8a,9,10-octahydro-phenanthren-2-yl ester ***4***.
Colorless oil;

^{1}H NMR (CDCl3, 300 MHz) 1.14 (3H, s, H-11), 1.17 (3H, s, H-12), 1.46 (3H, s, H-13), 2.11 (3H, s, H-18), 1.29 (3H, d, J = 7.1 Hz, H-15), 1.31 (3H, d, J = 7.1 Hz, H-16), 3.12 (1H, sept, J = 6.8 Hz, H-14), 6.66 (1H, d, J = 8.5 Hz, H-3), 6.80 (1H, d, *J* = 8.5, H-4);

^{13}C NMR (CDCl3, 300 MHz) 141.1 (C-1), 147.9 (C-2), 118.0 (C-3), 124.1 (C-4), 141.1 (C-4a), 27.5 (C-4b), 36.7 (C-5), 74.7 (C-6), 78.6 (C-7), 28.2 (C-8), 53.5 (C-8a), 29.9 (C-9), 24.6 (C-10), 19.4 (C-11), 20.7 (C-12), 25.7 (C-13), 15.8 (C-14), 24.9 (C-15), 25.72 (C-16), 168.2 (C-17), 16.9 (C-18),

Benzoic acid 7-hydroxy-1-isopropyl-4b,8,8-trimethyl-4b,5,6,7,8,8a,9,10-octahydro-phenanthren-2-yl ester ***5***.
Colorless oil;

^{1}H NMR (CDCl3, 300 MHz) 1.12 (3H, s, H-11), 1.14 (3H, s, H-12), 1.46 (3H, s, H-13), 1.30 (3H, d, J= 7.0 Hz, H-15), 1.31 (3H, d, J = 7.0 Hz, H-16), 3.12 (1H, sept, J = 6.9 Hz, H-14), 6.74 (1H, d, J = 8.5 Hz, H-3), 6.91 (1H, d, J = 8.5 Hz, H-4);
^{13}C NMR (CDCl3, 300 MHz) 140.1 (C-1), 147.9 (C-2), 118.2 (C-3), 124.1 (C-4), 141.1 (C-4a), 29.5 (C-4b), 32.0 (C-5), 24.7 (C-6), 78.4 (C-7), 34.4 (C-8), 53.2 (C-8a), 29.8 (C-9), 24.8 (C-10), 19.4 (C-11), 20.4 (C-12), 25.0 (C-13), 15.5 (C-14), 24.6 (C-15), 24.8 (C-16), 164.0 (C-17), 130.6 (C'1), 130.1 (C'3;C'5), 133.7 (C'4),

Benzoic acid 6,7-dihydroxy-1-isopropyl-4b,8,8-trimethyl-4b,5,6,7,8,8a,9,10-octahydro-phenanthren-2-yl ester ***6*****.**
Colorless oil;

^{1}H NMR (CDCl3, 300 MHz) 1.13 (3H, s, H-11), 1.16 (3H, s, H-12), 1.47 (3H, s, H-13), 1.33 (3H, d, J = 7.0 Hz, H-15), 1.31 (3H, d, J = 7.0 Hz, H-16), 3.20 (1H, sept, J = 6.9 Hz, H-18), 6.76 (1H, d, J = 8.5 Hz, H-3), 6.91 (1H, d, J = 8.5 Hz, H-4);
^{13}C NMR (CDCl3, 300 MHz) 141.2 (C-1), 147.9 (C-2), 118.0 (C-3), 124.1 (C-4), 141.1 (C-4a), 25.5 (C-4b), 39.6 (C-5), 79.2 (C-6), 76.5 (C-7), 28.0 (C-8), 53.6 (C-8a), 29.6 (C-9), 24.4 (C-10), 19.5 (C-11), 19.9 (C-12), 25.9 (C-13), 16.3 (C-14), 24.9 (C-15), 24.8 (C-16), 164.2 (C-17), 130.6 (C'1), 130.1 (C'3;C'5), 133.7 (C'4).

DFT calculations

The analysis of the DFT reactivity indices of the reagents was performed in first time to understand the participation of these reagents in esterification reactions [31], as well as the regioselectivity [32]. The global DFT reactivity indices, namely electronic chemical potential, μ, chemical hardness, η, electrophilicity ω, and nucleophilicity N indices of diterpenes (**1** and **2**), Ac_2O and Benzoyl chloride were summarized in Table 1.

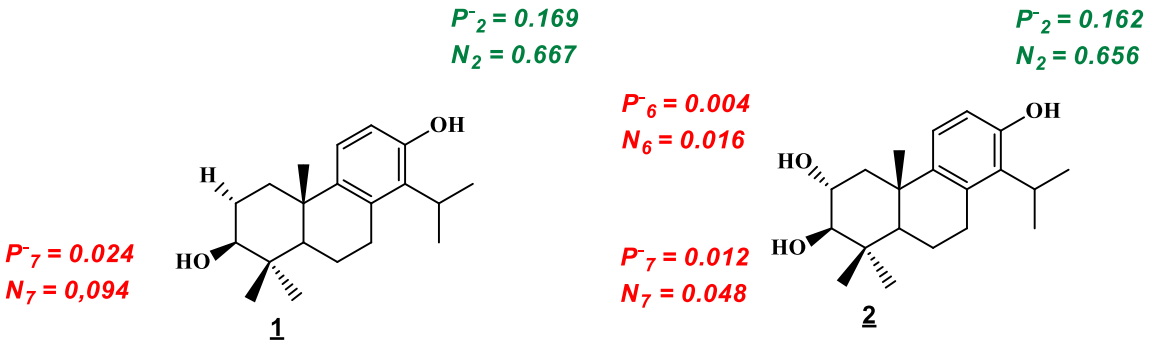
The electronic chemical potential (μ) of Ac_2O and Benzoyl chloride, respectively at -4.28 and -4.79 eV was lower than the diterpenes **1** and **2** at -2.67 and -2.63 eV respectively. These results showed that along the polar reaction, the global electron density transfer (GEDT) will be the flux from the diterpenes **1** and **2** rich on electrons towards Ac_2O and Benzoyl chloride.

Diterpenes **1** and **2** has a very low electrophilicity ω index [8], 0. 62, 0.60 eV respectively and a very high nucleophilicity N index [33, 34], 4.02, 4.06 eV, being classified as a marginal electrophile [35] and a strong nucleophile [33]. The electrophilicity ω index of the Ac_2O and Benzoyl chloride was 1.34 and 2.13 eV, respectively, being classified as strong electrophiles. Consequently, these diterpenes will participate as good nucleophiles in esterification reactions.

Table 1: DFT/B3LYP/6-31G(d) electronic chemical potential (μ), chemical hardness (η), electrophilicity (ω) and nucleophilicity (N) values, in eV, of diterpenes **1** and **2**, Ac_2O and Benzoyl chloride.

	η	μ	w	N
Diol	5.68	-2.67	0.62	4.02
Triol	5.68	-2.63	0.60	4,06
Ac_2O	6.80	-4.28	1.34	1.85
Benzoyl chloride	5.39	-4.79	2.13	2.04

Interestingly, the esterification reaction involving phenolic group was favored than hydroxyl group. These results could be analyzed the local nucleophilicity N_k [36] at O-2, O-6 and O-7 positions of the two diterpenes. Analysis of the corresponding local values indicated that the O-2 position of the diterpenes **1**, **2**, N_2 = 0. 667, 0.656 eV respectively (Scheme 4) was more nucleophilically than the O-6 of diterpene **1** and O-6, O-7 position of diterpenes **2**. Consequently, the formation of the –C2-OCO- single bond along the nucleophilic attach of diterpenes will be more favored than the formation of -C6-OCO- and -C7-OCO- single bond.



Scheme 4: ASD of the radical cations and nucleophilic P^-_k Parr functions of diterpenes **1** and **2**

The electrostatic potential is a real property, a physical observable. It can be obtained computationally [37]. While it has been used to interpreting, and predicting the regioselectivity[38]. Regions where V(r)>0 can be expected to be attracted favorably, at least initially, to negative portions of other molecules, while V(r) < 0 predicts attractive interactions with positive portions. In this part, we obtain V(r) with the density functional B3LYP/6-31(d). (figure 1)

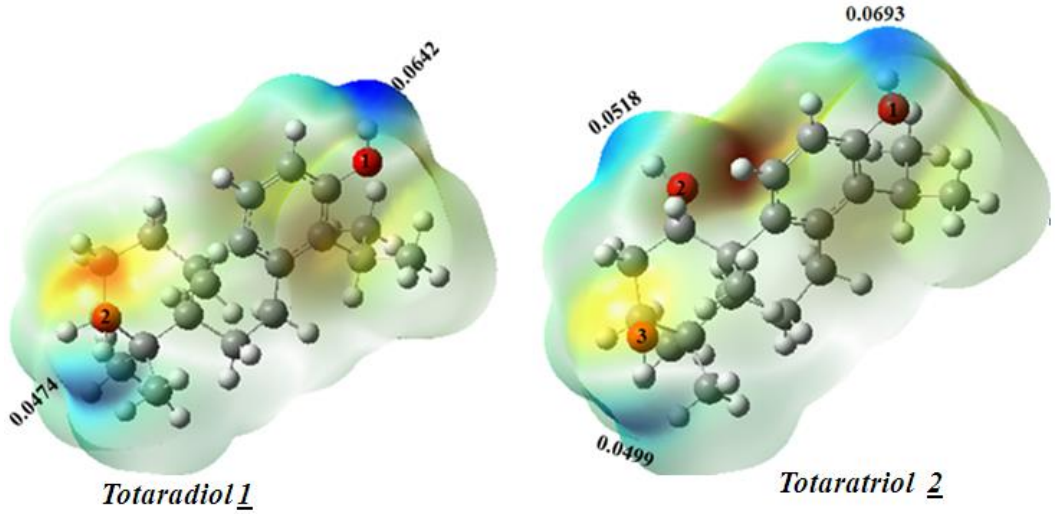
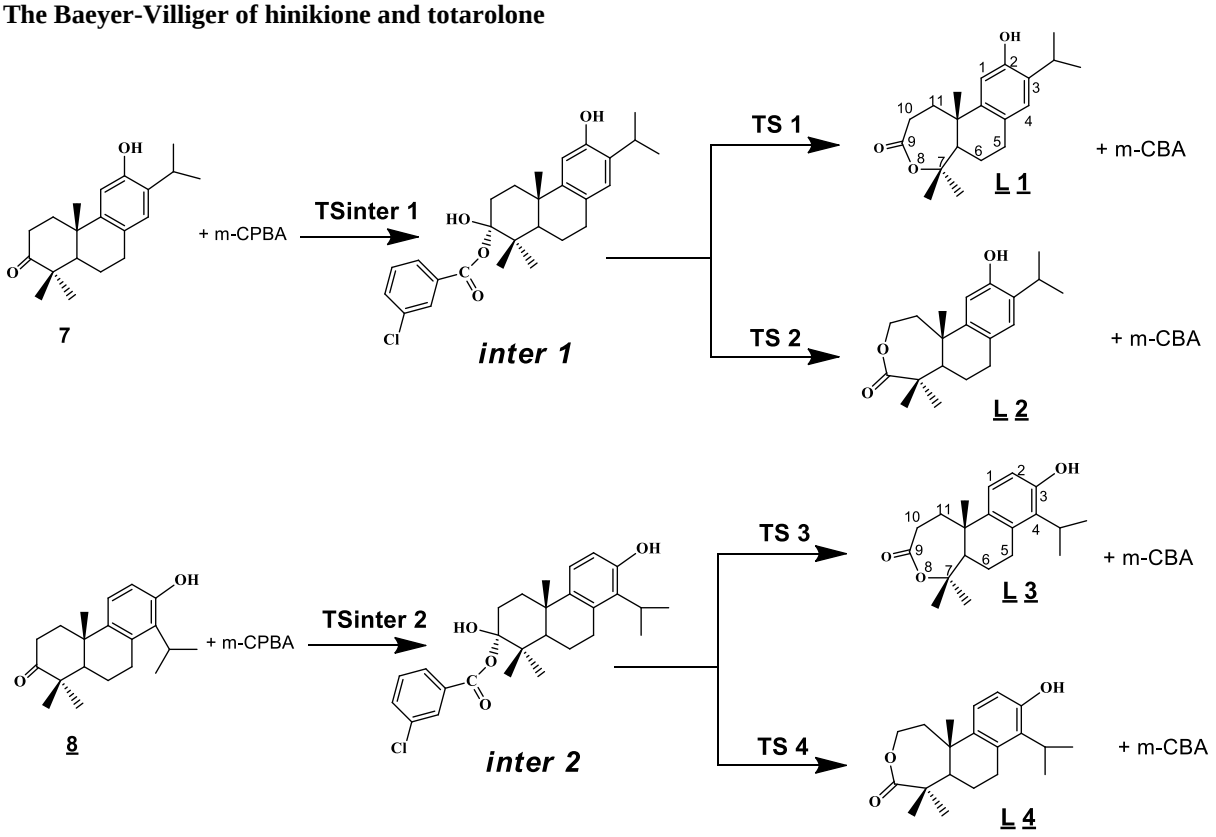


Figure 1: Calculated electrostatic potential on the 0.001 au surface of totaradiol and totaratriol in kcal/mol. We can have observed from figure 1 that surface map value of hydrogen H1 in totaradiol and totaratriol are (0.0642 and 0.0693 respectively) is great than anther hydrogen, indicating that the oxygen O1 is very nucleophilic atom than anther oxygens, the fact that these reactions were regiospecific.

The Baeyer-Villiger (B.V) oxidation

In this section, we aim at modelling the complete BV reaction mechanism of Hinikione **7** and totarolone **8** by m-CPBA, catalyzed by trifluoroacetic acid in dichloromethane, at reliable levels of theory.

The Baeyer-Villiger of hinikione and totarolone



Scheme 5. Competitive regioisomeric pathways associated with the Baeyer-Villiger reactions of hinikione **7** and totarolone **8**.

What is the origin of the *regio*selectivity of Baeyer-Villiger reaction?

The values of the energy and the relative energy ones of the stationary points involved in the Baeyer-Villiger reaction of hinikione **7** and totarolone **8** by m-CPBA are summarized in Table 2. The energy profile of the Baeyer-Villiger reaction of hinikione **7** and totarolone **8** are given in Figure 2.

Table 2. B3LYP/6-31G(d) total (E, in a.u) and relative [a] energies (ΔE, in kcal mol^{-1}) in dichloromethane of the stationary points involved in the Baeyer-Villiger reaction of hinikione **7** and totarolone **8.**

System	E (u.a)	ΔE (Kcam/mol)
7+m-CPBA	-1884.89774	----------
TSinter 1	-1884.84124	35.45
Inter 1	-1884.84234	6.21
TS1	-1884.86784	18.76
TS2	-1884.08384	70.21
L1+ m-CBA	-1885.06194	-81.32
L2+ m-CBA	-1884.00543	-67.58
8+ m-CPBA	-1884.88973	----------
TSinter 2	-1884.83521	34.21
Inter 2	-1884.88021	5.97
TS3	-1884.86282	16.88
TS4	-1884.78117	68.12
L3+ m-CBA	-1885.02106	-82.41
L4+ m-CBA	-1884.99916	-68.67

[a] Relative to **7** +m-CPBA and to **8** +m-CPBA

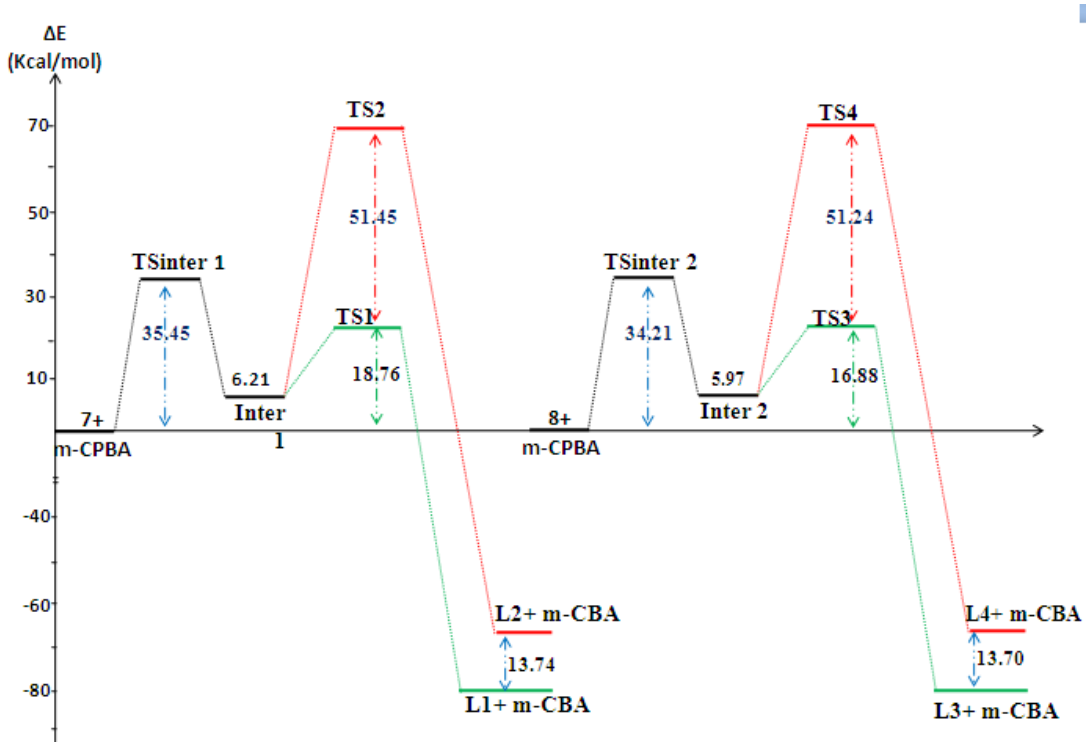


Figure 2. Energy profile (ΔE, in kcal mol^{-1}) of the Baeyer-Villiger reactions of hinikione **7** and totarolone **8**

The activation energies associated with the two reactive channels of the Baeyer-Villiger reaction between hinikione **7** and m-CPBA are 18.76 (**TS1**) and 70.21 (**TS2**) kcal mol^{-1}, the reaction being exothermic by between 67.58 and 81.32 kcal mol^{-1}. These energy results indicate that the ester L1 kinetically and thermodynamically preferred, the activation energies associated with TS3 and TS4 are 16.88 kcal mol-1 and 68.12 kcal mol-1, respectively and reaction energies associated with L3 and L4 are -82.41 kcal mol-1 and -68.67 kcal mol-1, respectively. Which shows that the formation of the L3 product is kinetically and thermodynamically favorable in good agreement with the experimental observations.

The geometries of the TSs involved in the BV reaction between hinikione **7** and totarolone **8** are given in Figure 3.

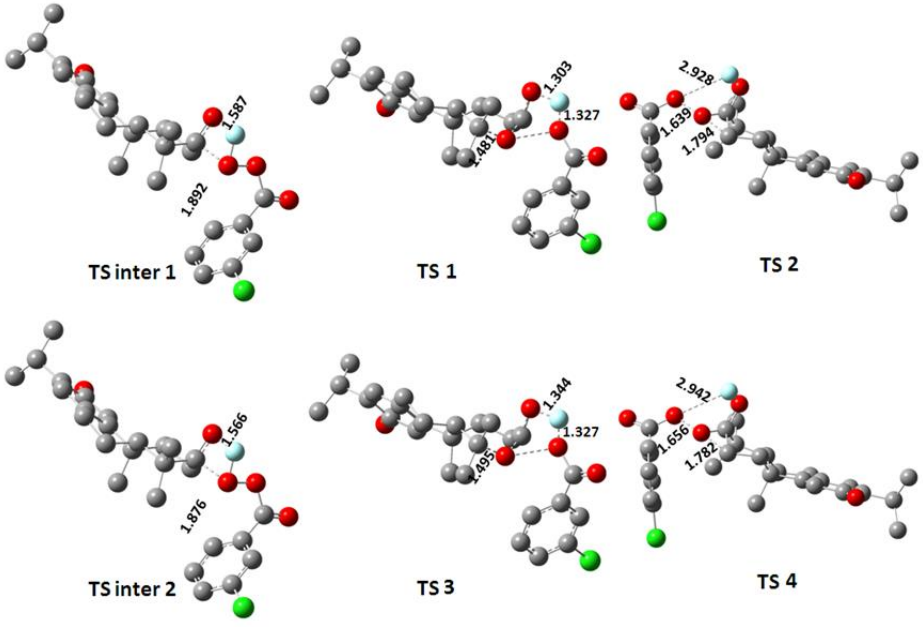


Figure 3. B3LYP/6-31G(d) optimized structures of the TSs of the BV reaction of hinikione **7** and totarolone **8**. Lengths are given in Angstrom.

The lengths of the C-O and O-H forming bonds at the TSs are 1.481 and 1.303 A at **TS-L1**, 1.794 and 2.928 A at **TS-L2**. These geometric parameters suggest an asynchronous bond formation process along the most favorable regioisomer L1 but an almost synchronous one along the regioisomer L1.

Understanding the *regio*selectivity of Baeyer-Villiger reaction using electrostatic potential V(r)

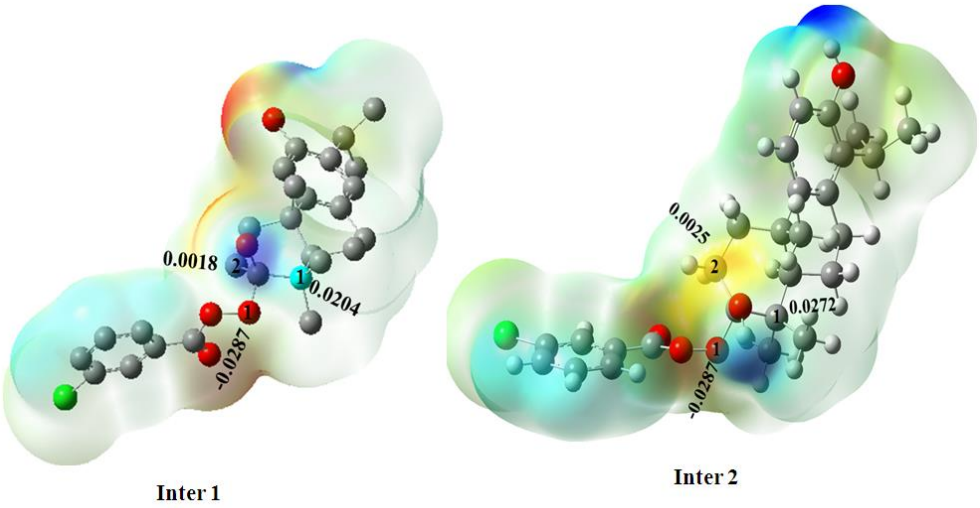


Figure 4. MEP surface for the lowest conformer of inter 1 and inter 2. Red regions of the map are the most electron-rich regions of the molecule and blue regions are electron poor. Order of increasing electron density is blue<green<yellow<orange<red.

Analysis surface potential of the intermediates (inter 1 and inter 2) shows that the density of the C1 atom (0.0204, 0.0272) is larger than the density of the C2 atom (0.0018, 0.0025) which indicates an interaction between oxygen O1 and C1 carbon is more favourable.

Conclusion

The reactions between totaradiol 1 and totaratriol 2 with benzoyl chloride or acetic anhydride in pyridine as solvent yielded four ester derivatives (3, 4, 5 and 6). The results showed that these reactions were regioselectives. In addition, DFT calculations were performed to rationalize the experimental results. The regioselectivity of the esterification reactions were confirmed by the analysis of Parr functions at both nucleophilic reagents. An exploration of the PES associated with the B V oxidation reaction indicates that it takes place through a two-step mechanism. These B V oxidations reactions have high regioselectivity. The strong exothermic character of these reactions makes the formation of lactones irreversible and we show that the formation of the lactones **L1** and **L3** is kinetically and thermodynamically favorable in good agreement experimental result.

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