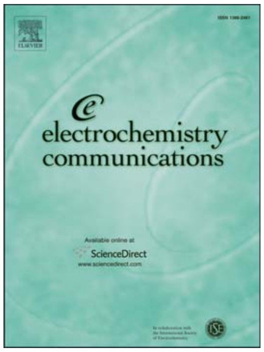

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PII: S1388-2481(16)30035-2
DOI: doi: 10.1016/j.elecom.2016.02.018
Reference: ELECOM 5649

To appear in: *Electrochemistry Communications*

Received date: 22 January 2016
Revised date: 22 February 2016
Accepted date: 22 February 2016

Please cite this article as: Belen Batanero, Javier Recio, Fructuoso Barba, One-pot anodic lactonization of *Fenchone* and *Menthone* and electrosynthesis of a new magnolione analogue, *Electrochemistry Communications* (2016), doi: 10.1016/j.elecom.2016.02.018

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One-pot Anodic Lactonization of *Fenchone* and *Menthone* and Electrosynthesis of a New Magnolione Analogue

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Abstract

The terpenoid cycloalkanones *Fenchone* and *Menthone* have been oxidized at a platinum anode under neutral and alkaline electrolyte conditions. When $NaClO_4$ was used as electrolyte, *Fenchone* (**1a**) afforded 1-isopropyl-4-methyl-2-oxa-bicyclo[2.2.1]heptan-3-one, and *Menthone* (**1b**) provided the stable lactone 6-isobutyl-4-methyl-tetrahydropyran-2-one, both in good yield. When using Na_2CO_3 as electrolyte, the oxidation of **1a** gave the fragrance-analogue 2,2-dimethyl-3-(2-oxopropyl) cyclopentanone in only one-pot. Mechanism proposals are presented.

Keywords: Anode, six-membered Lactones, Electrolytes, Fenchone and Menthone, Amperometric conditions, rearrangement, jasmonoid-like cyclopentanone

1. Introduction

The terpenoid lactones have been for centuries isolated from natural sources such as *Ginkgo biloba* leaves[1] or *Toxicodendrum capense*.[2] These compounds have demonstrated anti-stress and antidepressant therapeutic activity.[1] Many of them, such as the tetronic acid (furan- 2,4-dione) are highly valued cyclic esters, claimed as potent insecticidal, nematocidal or acaricidal agents, as well as exhibiting remarkable antifungal activity.[3] Lactones have been used as fertilizers,[4,5] or even in the treatment for depigmentation.

Other lactones isolated from natural products[6] have interest due to their aromatic properties such as ambrettolide from ambrette plant, or cyclopentadecanolide that is the second largest macrocyclic musk in tonnage terms. δ-Decalactone is used to give a fruity note (peach, coconut). Coumarin is presented in newly mown and its sweet, hay-like note is used widely in perfumery.

Electrochemical technology can be used to replace toxic or dangerous oxidizing or reducing reagents or can be used also for the *in-situ* production of unstable and hazardous reagents.[7] Electrosynthesis reduces energy consumption and is considered a clean and efficient synthetic methodology. The “electron” as reagent minimizes the number of steps as compared to conventional processes, decreasing pollution caused by the use of chemicals.

The anodic oxidation of some cycloalkanones into lactones, under hydro-alcoholic media was studied in our research group.[8,9] Now we apply the electrochemistry as methodology in a similar procedure to convert terpenic ketones *Fenchone* and *Menthone* into interesting lactones, a cyclopentanone jasmonoid and other derivatives. Mechanism proposals for these reactions are presented.

2. Experimental Section

2.1 General Remarks

The electrolyses were carried out using a current supplier Promax Model FAC-662B. GC was performed in a HP model 5890 Series II chromatograph. IR spectra of the products were recorded as dispersions in KBr or NaCl films on a Perkin-Elmer FT-IR Frontier spectrometer. All melting points were measured with a Reichert Thermovar microhot stage apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$ or CD_3OD solutions with a Varian Unity 300 (300 MHz) spectrometer. Chemical shift values are given in ppm and δ scale relative to tetramethylsilane (TMS) as

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the internal standard. Mass spectra (EI, ionizing voltage 70 eV) were determined using a THERMOFISHER ITQ-900 DIP/GC-MSn mass-selective detector. Elemental analyses were performed on a Leco CHNS Model 932 analyzer. All starting materials were obtained from commercial sources and used without purification.

2.2 General Electrochemical Procedure.

The electrolyses were carried out at 20 ºC under constant current conditions (0.2 A). An undivided beaker-type cell equipped with a magnetic stirrer was employed. The solvent-supporting electrolyte (SSE) was either H_2O/EtOH (1:1) / 0.3 M $NaClO_4$ or / 0.3 M Na_2CO_3 solutions. As anode a platinum sheet (geometric area 8 cm^2) (1 cm separation of the cathode) was used.

In order to get a clean and reproducible surface the platinum electrode was heated in a flame and polished. As cathode a carbon plate was used. The anolyte was 60 mL of the SSE solution containing 2 x 10^{-3} mol of electroactive substrate **1**. The electrolyses were carried out during 3h and 45 min., which corresponds to a 700% circulated charge (2702 C) in a 2F/mol process.

Once the electrolysis was finished, the EtOH was removed under reduced pressure. The residue was extracted three times with ether and the organic phase dried over Na_2SO_4 and concentrated by evaporation. The resulting solid (or oil) was chromatographed on a GC-MS (HP-5 cross linked 5% PhMe silicone) 30m-0,25mm-0.25μm chromatographic column) instrument and a silica gel (18 × 3 cm) column using chloroform (**2a**) or hexane/EtOAc (30/1) (**3a**, **4a**) as eluents. In order to isolate the water-soluble products (hydroxyl derivatives), the aqueous phase (slightly alkaline with Na_2CO_3 as electrolyte) was neutralized, ether extracted and dried. All the products were identified by their spectroscopic data (see below). The characterization of the known compounds **4b** and **5b** was completed with their MS spectra. Yields are defined as the ratio between the number of moles of product and the number of moles of the reactant consumed taking into account the stoichiometric coefficients.

1-Isopropyl-4-methyl-2-oxa-bicyclo[2.2.1]heptan-3-one (**2a**): Oil. B.p.: 244-247 ºC. IR (NaCl) ν/cm^{-1} = 2962, 2929, 2872, 1732, 1464, 1277, 1161, 1095, 951. ^{1}H NMR (300 MHz; $CDCl_3$): δ (ppm): 1.27 (s, 3H), 1.35 (d, 6H, J= 7.2 Hz), 1.53 (m, 2H), 1.87 (m, 3H), 2.07 (m , 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ (ppm): 20.4, 24.6, 26.2, 28.3, 35.1, 37.0, 43.7, 44.9, 84.1, 176.7. MS m/z (relative intensity) IE: 168 (M$^+$, 19), 153 (12), 125 (13), 81(84), 67(100). Anal. Calc. for C_{10} H_{16} O_2: C, 71.43; H, 9.52. Found: C, 71.06; H, 9.72.

1,4,4-Trimethyl-3-oxa-bicyclo-[3.2.1]octan-2-one (**2a´**): MS m/z (relative intensity) IE: 168 (M$^+$, 100), 151 (54), 111 (93), 109 (12).

Ethyl 3-hydroxy-3-isopropyl-1-methylcyclopentane carboxylate (3a): Oil. B.p.: 278-280 ºC. IR (KBr) ν/cm^{-1} = 3505, 2972, 2941, 2873, 1725, 1446, 1375, 1119, 1025, 935. ^{1}H NMR (300 MHz; $CDCl_3$) δ (ppm): 1.15 (d, 6H, J= 3.0 Hz), 1.21 (t, 3H, J= 7.2 Hz), 1.22 (s, 3H), 1.51 (m, 2H), 1.73 (m, 3H), 1.84 (bs, 1H), 2.13 (m, 2H), 4.08 (q, 2H, J= 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 14.1, 24.9, 26.5, 28.0, 28.3, 37.7, 38.2, 49.2, 49.6, 60.5, 71.6, 178.7. MS m/z (relative intensity) IE: 214 (M$^+$, 6), 197(22), 156(28), 141(28), 123(52), 115(80), 86 (100), 81 (55), 67 (61), 59 (75). Anal. Calc. for C_{12} H_{22} O_3: C, 67.29; H, 10.28. Found: C, 66.95; H, 10.61.

2,2-Dimethyl-3-(2-oxopropyl)cyclopentanone (4a): Oil. B.p.: 264-268 ºC. IR (NaCl) ν/cm^{-1} = 2968, 2928, 2873, 1738, 1715, 1470, 1381, 1362, 1173, 1103, 1055. ^{1}H NMR (300 MHz; $CDCl_3$) δ (ppm): 0.78 (s, 3H), 0.97 (s, 3H), 1.47 (m, 2H), 2.15 (s, 3H), 2.22 (m, 2H), 2.51 (m, 2H), 2.63 (m, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 17.9, 22.0, 24.7, 30.0, 35.7, 41.8, 43.5, 46.8, 207.0, 221.8. MS m/z (intensidad relativa) IE: 168 (M$^+$, 13), 151(20), 111(100), 97(20), 67(35), 55(30). Anal. Calc. for C_{10} H_{16} O_2: C, 71.43; H, 9.52. Found: C, 71.34; H, 9.58.

(*Z*)-6-Isobutyl-4-methyltetrahydropyran-2-one (2b): Oil, B.p.: 249-251 ºC [Lit. **[**10,11] B.p.: 110 ºC (5 torr)]. IR (NaCl) ν/cm^{-1} = 2960, 2931, 2873, 1734, 1461, 1379, 1239, 1097, 988. ^{1}H NMR (300 MHz; $CDCl_3$) δ (ppm) 0.90 (d, 6H, J=6.7 Hz), 1.00 (d, 3H, J= 5.9 Hz), 1.23 – 1.35 (m, 3H), 1.62 (m, 1H), 1.86 (dd, 2H, J_1= 4.87 Hz, J_2=12.7 Hz), 2.00 (d, 1H, J=11.5 Hz), 2.65 (d, 1H, J=11.7 Hz), 4.30 (m, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 21.7, 22.0, 23.0, 23.9, 26.7, 37.5, 38.1, 45.2, 78.8, 171.6. MS m/z (relative intensity) IE: 170 (M$^+$, 60), 153 (9), 113 (3), 95 (3), 85 (8), 69 (10), 67 (5), 56 (3).

Ethyl 5-hydroxy-3,7-dimethyl octanoate (3b): Oil, [Lit.[12] B.p.: 100 -105 ºC (2 torr)]. IR (NaCl) ν/cm^{-1} = 3512, 2958, 2925, 2874,1735, 1435, 1382, 1249, 1123, 945. ^{1}H NMR (300 MHz; $CDCl_3$) δ (ppm): 0.90 (d, 6H, J= 6.7), 0.95 (d, 3H, J= 6.6 Hz), 1.23 (t, 3H, J= 7.3 Hz), 1.23 – 1.35 (m, 3H), 1.62 (m, 1H), 1.86 (m, 2H), 2.00 (m, 1H), 2.65 (m, 1H), 3.20 (m, 1H), 4.10 (q, 2H, J= 7.3 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 14.3, 20.3, 23.4, 25.4, 29.7, 40.7, 42.6, 44.6, 60.2, 73.2, 172.9. MS m/z (relative intensity) IE: 216 (M$^+$, 3), 199 (100), 154 (16), 153 (14), 115 (67), 109 (18), 87 (90), 69 (46), 67 (10).

2-Ethoxy-2-isopropyl-5-methyl-cyclohexanone[13] (**4b**): MS m/z (relative intensity) IE: 198(M$^+$, 44), 155(M$^+$-^{i}Pr, 20), 153 (M$^+$-EtO, 18), 137(15), 115(98), 109 (72), 95(17), 87(100), 69(56).

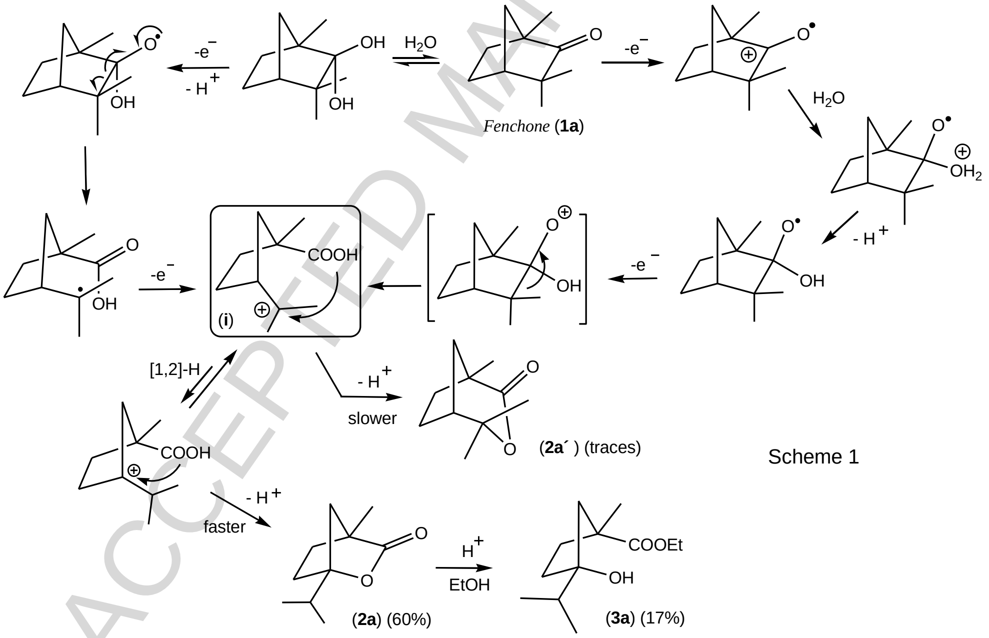
2-Hydroxy-2-isopropyl-5-methyl-cyclohexanone[14] (**5b**): MS m/z (relative intensity) IE: 170 (M$^+$, 17), 153(M$^+$-17, 30), 152 (M$^+$-18, 19), 137(23), 127(M$^+$-^{i}Pr, 5), 110(44), 109 (M$^+$-18, 40), 95(100), 87(17), 85(18), 69(32).

3. Results and discussion

Contrary to the Baeyer-Villiger oxidation of cycloalkanones, where the main product is the corresponding ω-lactone, in the anodic discharge of these substrates the final lactone nature depends on the stability of the electrogenerated carbocation intermediates.

3.1 Anodic oxidation of *Fenchone* (**1a**) and *Menthone* (**1b**) under hydro-alcoholic/$NaClO_4$ solvent-supporting electrolyte system (SSE):

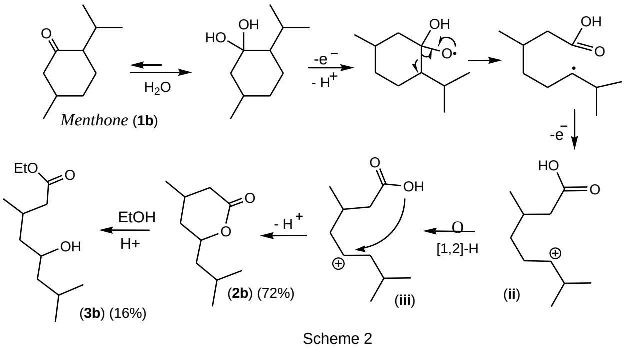
The anodic oxidation of 1,3,3-trimethylbicyclo [2.2.1]heptan-2-one (**1a**), well known as *Fenchone*, at a Pt anode and under the constant current value of 0.2 A (amperometric conditions) (see experimental section) afforded 1-isopropyl-4-methyl-2-oxa-bicyclo[2.2.1]heptan-3-one (**2a**) as the main product (60% yield) through the mechanism proposals shown in Scheme 1. The first step involves either the oxidation of the hydrate of Fenchone (**1a**) or the direct oxidation of **1a**. A ketone hydrate would be expected to be easier to oxidize than the ketone itself since the hydrate radical cation would be rapidly deprotonated in the protic medium and a sp^3 oxygen is less electronegative than a sp^2 oxygen. The two mechanisms lead to a common intermediate, the tertiary carbocation **i**, the cyclization of which to lactone **2a´** (trace amounts, see MS) would be slower than the [1,2]-H shift leading to the major product, lactone **2a**. The hydroxy ester **3a** (17% yield) would come from the ethanolysis of lactone **2a** and/or from the oxidation of the hemiacetal of **1a** (not shown). The current efficiency (c.e.) for the products formation was 14%. The main electrochemical process was the oxidation of ethanol, present in large excess with respect to **1a**, and easier to oxidize than **1a** and as easy to oxidize as the hydrate of **1a**.



Scheme 1. Fenchone oxidation pathway to lactone **2a** in $NaClO_4$ as electrolyte.

When the electrolysis is performed with 5-methyl-2-isopropyl-cyclohexanone (*Menthone*) (**1b**) under the same experimental conditions, the stable lactone 6-isobutyl-4-methyl-tetrahydropyran-2-one (**2b**) was obtained as the major product (72% yield) together with the δ-hydroxy ester **3b** (16% yield) (13% c.e. for the two products) as indicated in Scheme 2.The mechanistic proposals for the oxidation of Menthone (**1b**) involve the same steps as those in Scheme 1. The two secondary carbocations **ii** and **iii** are in equilibrium, but the cyclisation of **iii** to the six-membered ring lactone **2b** would be much faster than the cyclisation of **ii** leading to a seven-membered ring lactone (not shown).

It is interesting to note that, according to the ^{1}HNMR spectrum of **2b**, only the more stable *cis* isomer has been obtained (by comparison with the published spectra of a mixture of *cis* and *trans*[10] **2b** and of *cis*[11] **2b**).This means that the formation of lactone **2b** is under thermodynamic control, giving the more stable stereoisomer having the methyl and the *i*-propyl groups in the equatorial orientation.

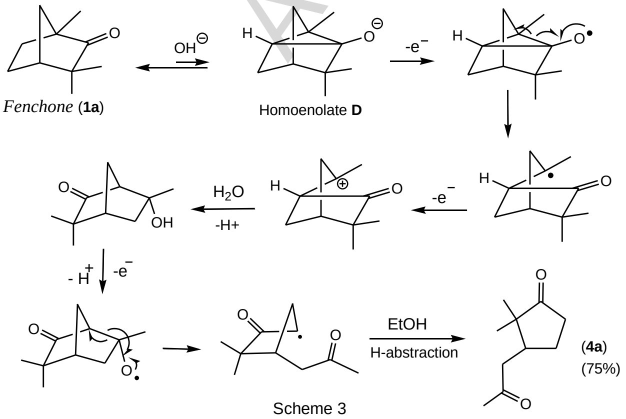


Scheme 2. Menthone oxidation pathway to lactone **2b** in $NaClO_4$ as electrolyte.

In order to study and compare the reaction pathways followed by these substrates at the anode, the employ of a starting basic pH conditions was also considered.

3.2 Anodic oxidation of *Fenchone* (**1a**) and *Menthone* (**1b**) under hydro-alcoholic/Na_2CO_3 solvent-supporting electrolyte system (SSE):

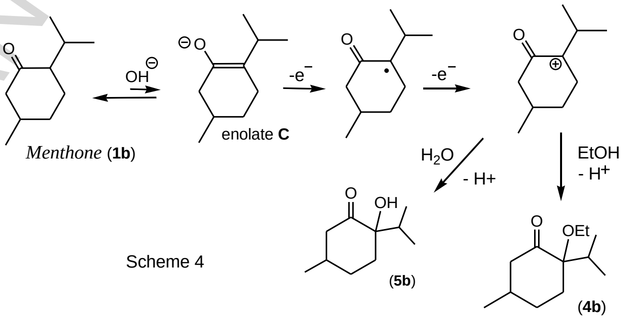
When anodic oxidation of **1a** was performed in the presence of an alkaline electrolyte medium, the nature of the main obtained product was completely different. In this case, a 2,3-disubstituted cyclopentanone **4a** was isolated in good yield. A mechanism proposal is presented in Scheme 3. It involves the oxidation of the homoenolate of *Fenchone*. Although homoenolisation of 2-norbornanone structures have been carried out and studied at high temperature, [15] it is possible that a small amount of homoenolate **D** could have been formed. Such a homoenolate would be easier to oxidized than EtOH, and after C-C homolytic cleavage of the obtained radical, further oxidation to a tertiary carbocation and a final hydrogen abstraction from ethanol (that would be faster than the oxidation of the radical to a carbocation next to an electron-attracting carbonyl) should afford **4a** through the steps shown in Scheme 3.



Scheme 3. Fenchone oxidation pathway to substituted cyclopentanone **4a** in Na_2CO_3 as electrolyte.

Cyclopentanone readily undergoes aldol condensation with a variety of aldehydes to give the 2-alkylidene cyclopentanones. These have jasmine-like odours, but are no longer used in perfumery since it was discovered that they have the potential to cause skin sensitization. The saturated products, such as *Magnolione*,[16] are safe and are used to give jasminic, fruity or floral odours in fragrances. The obtained 2,2-dimethyl cyclopentanone **4a** is a potential target molecule to be applied as analogue of such interesting saturated cyclopentanone derivatives.

The oxidative electrolysis of **1b** under these alkaline conditions (rationalized in Scheme 4) provides the α-ethoxy and α-hydroxy substituted cyclohexanones **4b** and **5b** respectively. In a basic medium these compounds are most probably formed by the oxidation of the thermodynamic enolate **C** (the more substituted enolate) that after a 2e- oxidative process affords a tertiary carbocation that is finally attacked by the solvent molecules.



Scheme 4. Menthone oxidation pathway to substituted cyclohexanones **4b** and **5b** in Na_2CO_3 as electrolyte.

However this reaction, under alkaline conditions, has poor interest because it does not proceed with selectivity. A mixture of the lactone **2b**, and cyclohexanones **4b** and **5b**, together with other minor products, are obtained in the oxidation of *Menthone* at pH=9.

4. Conclusions

The use of $NaClO_4$ as electrolyte in the anodic oxidation of the terpenoid cyclohexanones *Fenchone* (**1a**) and *Menthone* (**2a**) allowed their conversion to the interesting six-membered lactones **2a** and **2b** respectively in very good yield. When Na_2CO_3 was used as the electrolyte (pH=9), a new *Magnolione* fragrance analogue, cyclopentanone **4a**, was obtained from **1a** in 75% yield. Mechanisms have been proposed for the formations of these products.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

The authors gratefully acknowledge the financial support of the University of Alcala-CCG2015/EXP-031.

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Graphical Abstract

One-pot Anodic Lactonization of *Fenchone* and *Menthone* and Electrosynthesis of a New *Magnolione* Analogue

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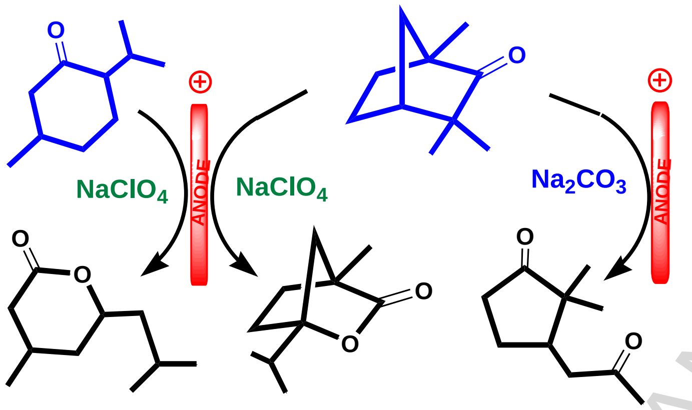

Highlights:

- Green and good-yield formation of valuable δ-lactones by anodic oxidation. Dependence of the type of products on the electrolyte.
- Electrosynthesis of a Magnolione analogue in only one-step.
- Electrolyte dependence in the mechanism pathway of electrogenerated terpenoid cation radicals.
- Not-expensive and environmentally sustainable procedure to convert alkylated cyclohexanones into new framework structures at the anode.