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A Novel and Efficient Synthesis of Tocopheryl Quinones by Homogeneous and Heterogeneous Methyltrioxorhenium/Hydrogen Peroxide Catalytic Systems

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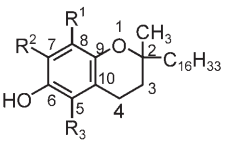
Abstract: A convenient and efficient application of heterogeneous poly(4-vinylpyridine), poly(4-vinylpyridine *N*-oxide), and polystyrene/methylrhenium trioxide systems for the selective oxidation of tocopherols and tocopherol derivatives to the corresponding *ortho*- and *para*-tocopherylquinones is described. Environment friendly, easily available, and low-cost hydrogen peroxide (H_2O_2) was used as the oxygen atom donor. The antiviral activity of the newly synthesized tocopherylquinones and their parent tocopherols against influenza A virus is also reported. On the basis of the biological assay, the activity of tocopherols against influenza virus is higher than that showed by the corresponding tocopherylquinones, thus suggesting, for the first time, a drawback effect of the oxidative metabolism on the antiviral activity of these compounds.

Keywords: antiviral agents; heterogeneous catalysis; homogeneous catalysis; hydrogen peroxide; quinones; rhenium

Introduction

Tocopherols (vitamin E) are a family of natural phenols derived from shikimic acid, which share a common structure characterized by a chromanol head and an isoprenic side chain.[1] There are four different tocopherols, named α-, β-, γ-, and δ-tocopherols, that differ in the number and position of methyl groups on the chromanol head (Figure 1). Due to their high antioxidant activity,[2] tocopherols have been used in medications, health-care and cosmetic formulations and as stabilizers in plastic packing.[3] Since the major biological role of tocopherols appears to be that of chain breaking agents in inhibiting lipid peroxidation in membranes,[4] much interest has been devoted to the products of their oxidations with organic and inorganic oxidants to gain data on the mechanism of action in tissues and lipids.[5] Tocopherols are oxidized *in vitro* by a mono-electronic mechanism to a stable tocopheroxyl radical[6] which, in turn, depending on the experimental conditions, can trap other alkyl radicals to form derivatives at both the 6- and the 5-positions.[7] The tocopheroxyl radical can also polymerize to dihydroxy dimers,[8] spirodimers and spirotrimers.[9] The loss of a second electron from the tocopheroxyl radical leads to quinone methide species and successively *ortho*- and *para*-tocopherylquinones[10] and epoxytocopherylquinones are formed.[11]



α-tocopherol (α-T): $R^1 = R^2 = R^3 = CH_3$
β-tocopherol (β-T): $R^1 = R^3 = CH_3$; $R^2 = H$
γ-tocopherol (γ-T): $R^1 = R^2 = CH_3$; $R^3 = H$
δ-tocopherol (δ-T): $R^1 = CH_3$; $R^2 = R^3 = H$

Figure 1. Structure of individual tocopherols in vitamin E.

Among the products of oxidation of tocopherols, quinones play a relevant role by modulating the biopotency of these substances.[12] As an example, α-tocopherol is oxidized *in vivo* to *para*-α-tocopherylquinone (*para*-α-TQ), that is an effective antioxidant with a low citotoxicity[13] and exerts a benefical effect on heart attacks, strokes,[14] muscular dystrophy[15] creatinuria, paralysis, weight loss and fetal resorbtion.[16]

γ-Tocopherol and δ-tocopherol are less readily oxidized *in vivo* than α-tocopherol,[17] the corresponding quinones being characterized by high biological activity. With the exception of stoichiometric oxidations with iron(III) chloride ($FeCl_3$), gold(III) chloride ($AuCl_3$) and silver nitrate ($AgNO_3$),[18,19] only few data are reported in the literature on the synthesis of tocopherylquinones from parent tocopherols, However, these procedures require severe experimental conditions, afford the desired products in very low yield, produce large amount of wastes and are not of a general efficacy for the preparation of *ortho*-tocopherylquinones. Thus, there is a considerable interest in the design of novel oxidative transformations of tocopherols to tocopherylquinones, especially with regard to catalytic procedures requiring the activation of environmental friendly hydrogen peroxide (H_2O_2) as primary oxidant.

A catalyst useful for this purpose is methyltrioxorhenium(VII) ($MeReO_3$, MTO),[20] which is step-wise converted by H_2O_2 into reactive monoperoxo [$MeRe(O)_2O_2$] (**A**) and bisperoxo [$MeReO(O_2)_2$] (**B**) η^2-rhenium complexes[21] that able to transfer one oxygen atom to substrate by a concerted mechanism. MTO, in combination with H_2O_2 has in recent years become an important catalyst for a variety of synthetic transformations.[22] Accordingly with this high reactivity, MTO is able to catalyze the oxidation of low reactive aromatic derivatives.[23,24] Heterogeneous rhenium catalysts, of the general formula $(polymer)_f/(MTO)_g$ (the f/g quotient express the ratio by weight of the two components), prepared by coordination of MTO on poly(4-vinylpyridine) (PVP2/MTO **I** and PVP25/MTO **II**) and poly(4-vinylpyridine *N*-oxide) (PVPN2/MTO **III** and PVPN25/MTO **IV**) 2% and 25% cross-linked with divinylbenzene or by microencapsulation with polystyrene (PS/MTO **V**) (Figure 2),[25] behave in a similar way.[26]

The reactivity and selectivity of catalysts (**I**–**IV**) might be finely tuned by the chemical and physical properties of the polymeric nitrogen and oxygen ligands.[27,28] A similar effect have been also obtained in a more complex family of microencapsulated catalysts, as in the case of catalyst (**VI**) (PS/MTO/L), prepared by encapsulation of the preformed adduct between MTO and 2-aminomethylpyridine (Figure 3).[29] Heterogeneous MTO compounds (**I**–**VI**) are efficient and selective catalysts for the oxidation of phenol and anisole derivatives,[30] cardanols (*n*-pentadecylphenols) from roasted cashew nut shell liquid (CNSL),[31] flavonoids,[32] lignins[33] and lignan derivatives[34] to the corresponding bioactive *ortho*- and *para*-benzoquinones. These reactions offer the advantages of easy and practical work-up procedures, with recovery of the catalyst by simple filtration without any substantial loss of activity over several successive runs. As a general reaction pattern, the oxidation of phenols under heterogeneous conditions proceeds through a concerted oxygen atom transfer from supported η^2-rhenium peroxo complexes (**A**) and (**B**) to substrate with formation of reactive 1,2-arene epoxide intermediates and subsequent oxiranyl ring opening, dehydration and further oxidation to corresponding quinone derivatives.[35]

A fine-tuned substituent effect on the regioselectivity of the oxidation (that is *ortho*- versus *para*-benzoquinones) was observed depending on the hindrance and position of substituents on the aromatic ring. *Para*-benzoquinones were selectively obtained in high yields during the oxidation of *para*-unsubstituted phe-

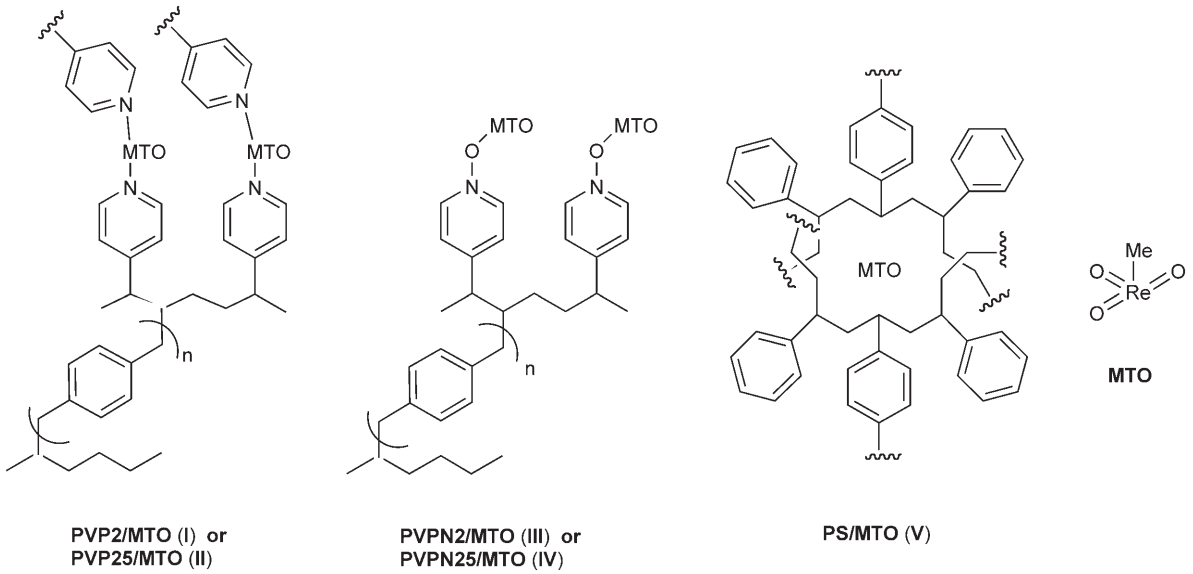


Figure 2. Schematic representation of the structure of poly(4-vinylpyridine), poly(4-vinylpyridine *N*-oxide), and polystyrene/methylrhenium trioxide (PVP/MTO, PVPN/MTO and PS/MTO, respectively) systems (**I**–**V**). n = % of divinylbenzene units.

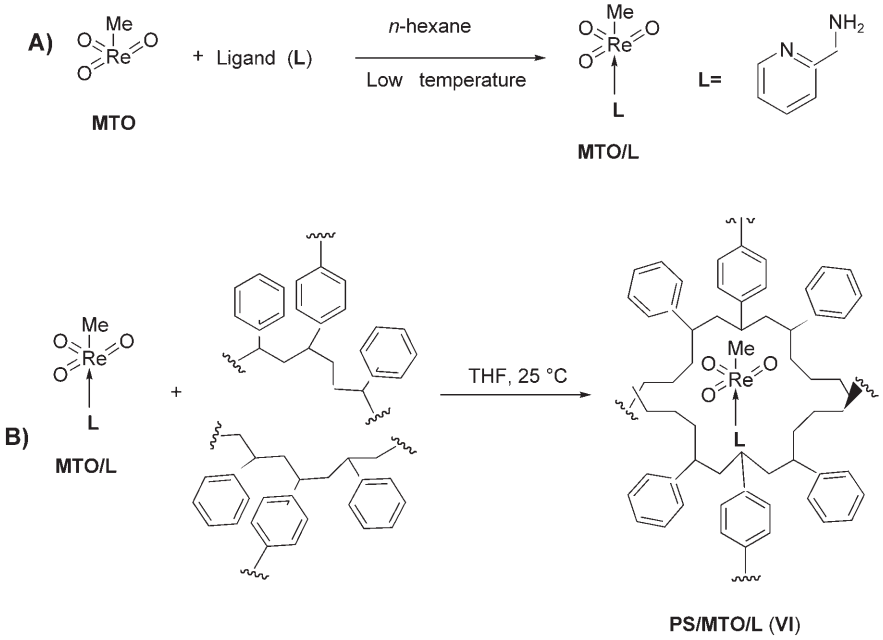


Figure 3. Schematic representation of the **PS/MTO/L** catalyst (**VI**) prepared by encapsulation with polystyrene of the complex between MTO and 2-aminomethylpyridine (**MTO/L**).

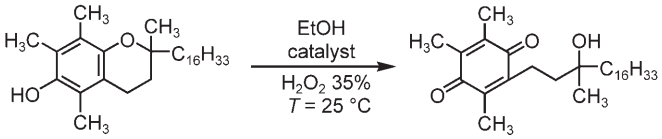
nols with small alkyl side-chains. Instead, *ortho*-benzoquinones became the main reaction products in the oxidation of *para*-substituted phenols, along with low amount of quinone methide derivatives.[36]

We report here that polymer-supported MTO catalysts (**I**–**VI**) may be used for the efficient and selective oxidation of tocopherols to the corresponding *ortho*- and *para*-tocopherylquinones with H_2O_2 (30% water solution) as environment-friendly primary oxidants. To the best of our knowledge this is the first example dealing with a general catalytic procedure for the synthesis of both *ortho*- and *para*-tocopherylquinones. The antiviral activity of tocopherylquinones and of their parent tocopherols against influenza A virus is also reported as an unprecedented example of the effect of vitamin E derivatives with a different oxidation state on the replication of respiratory viruses.

Results and Discussion

Initially, the oxidation of tocopherols with MTO, MTO/L and heterogeneous MTO catalysts (**I**–**VI**) was investigated using α-tocopherol (α-T) **1** as the most representative component of vitamin E. The reactivity of MTO is usually increased in the presence of an acidic medium. In this context, the use of acetic acid (AcOH) as solvent in the oxidation of phenols with MTO has been previously reported.[33] In our procedure we selected EtOH to avoid the formation of peroxyacetic acid,[34] the presence of which can influence the efficiency and selectivity of the transformation. As a general procedure, α-T **1** (1.0 mmol) was added to a suspension of heterogeneous catalysts (**I**–**VI**) (100 mg with a value of the catalyst loading factor of 1.0 for the oxidation of α-T and 0.5 for the oxidation of δ-T and γ-T; that is mmol of MTO for 1.0 g of support) in EtOH (5.0 mL) at room temperature. Hydrogen peroxide (6.0 mmol, 30% water solution) was added to the suspension in several batches and the mixture was stirred at room temperature for 10 h. The reaction time for the experiments was limited to 10 h to compare the efficiency of each catalytic system. In some representative cases (that is the most reactive catalysts) a quantitative conversion of substrate was also attained. The oxidations with homogeneous MTO and MTO/2-aminomethylpyridine complex (MTO/L) were performed under similar experimental conditions as references. The results of the oxidations are reported in Table 1. In some cases, the poor mass balance is presumably due to the formation of water-soluble, ring-opened products, that we have not recovered during the work-up of the reaction mixture. In the absence of the catalyst, less than 2% conversion of substrate took place under otherwise identical conditions. The catalysts were recovered at the end of the reaction after washing with EtOH and were used in successive oxidations under identical conditions (*vide infra*). Irrespective of the experimental conditions, the *para*-α-tocopherylquinone **2** (*pα*-TQ) was obtained as the only recovered product, besides unreacted substrate, in acceptable yield. This result may be attributed to the retained reactivity of the monoperoxo- and the bisperoxo-rhenium inter-

Table 1. Oxidation of α-tocopherol **1**.



1 2

Entry	Catalyst	Conversion [%]	Yield [%][a]
1	MTO	95	90
2	MTO/L[b]	52	44
3	PVP2/MTO (**I**)	60	53
4	PVP25/MTO (**II**)	69	67
5	PVPN2/MTO (**III**)	58	49
6	PVPN25/MTO (**IV**)	67	65
7	PS/MTO (**V**)	45	36
8	PS/MTO/L (**VI**)	50	43
9	PVP25/MTO (**II**)	>95	84[c]

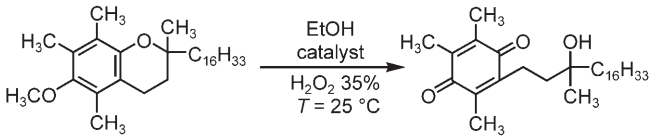
[a] Yield of **2** calculated after 10 h.
[b] L = 2-aminomethylpyridine.
[c] Yield of **2** calculated after 48 h.

mediates in heterogeneous systems. As a general reaction pattern, catalysts (**I–VI**) were less reactive than MTO, probably due to the presence of a kinetic barrier of the substrate to approach the supported rhenium complexes (Table 1, entry 1 *vs.* entries 3–8). It is worthy of note that poly(4-vinylpyridine) catalysts (**I–IV**) were more reactive than microencapsulated systems, compounds (**V**) and (**IV**) affording **2** in highest yield (Table 1, entries 4–6 *versus* 7 and 8). Concerning the poly(4-vinylpyridine) family, an enhancement of the value of the reticulation grade of the polymer increased both the reactivity and selectivity of the oxidation (Table 1, entry 4 *vs.* 3). A similar behaviour was observed with the poly(4-vinylpyridine *N*-oxide) resin (Table 1, entry 6 *vs.* 5). These data are in accordance with our previous findings on the effect of the reticulation grade of the polymer on the reactivity and selectivity of the catalyst.[37] In the case of the oxidation with microencapsulated catalyst (**VI**), the presence of 2-aminomethyl pyridine ligand increased both the reactivity and selectivity of the reaction with respect to (**V**) (Table 1, entry 5 *vs.* 6). The parent homogeneous catalyst MTO/L showed a reactivity and selectivity similar to (**VI**) (entry 2). To evaluate the synthetic utility of these procedures, the oxidation of **1** was repeated with the most active catalyst, compound (**II**), to obtain a quantitative conversion of substrate (48 h). Under these experimental conditions **2** was recovered in 84% yield (Table 1, entry 9).

In a test for checking the leaching of the catalysts, the oxidation of α-T **1** with two selected catalysts, compounds (**I**) and (**II**), was stopped at *ca.* 50% conversion. After removal of the catalyst the solution lost the catalytic activity. Moreover, both catalysts were stable enough to perform at least four recycling experiments in the oxidation of α-T **1** with similar conversion of substrate and product selectivity (Table 2, entries 1 and 2).

With the aim to evaluate the effect of substituents with different electronic properties on the oxidation of tocopherols, we further studied the oxidation of two derivatives of α-T **1**, 6-*O*-methyl-α-tocopherol (*O*Me-α-T) **3** and 6-*O*-acetyl-α-tocopherol (α-tocopherol acetate, *O*Ac-α-T) **4**, under similar experimental conditions. The results of the oxidations are reported in Table 3 and Table 4. The presence of the

Table 3. Oxidation of 6-*O*-methyl-α-tocopherol **3**.



3 2

Entry	Catalyst	Conversion [%]	Yield [%][a]
1	MTO	75	64
2	MTO/L[b]	70	55
3	PVP2/MTO (**I**)	67	54
4	PVP25/MTO (**II**)	75	62
5	PVPN2/MTO (**III**)	60	39
6	PVPN25/MTO (**IV**)	70	59
7	PS/MTO (**V**)	65	52
8	PS/MTO/L (**VI**)[b]	70	60
9	PVP25/MTO (**II**)	>95%	81[c]

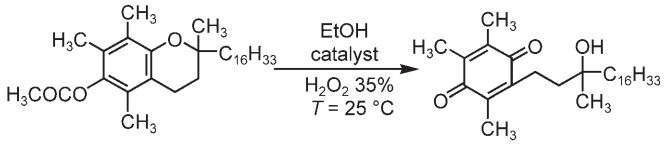
[a] Yield of **2** calculated after 10 h.
[b] L = 2-aminomethylpyridine.
[c] Yield of **2** calculated after 48 h.

Table 2. Stability of catalysts (**I**)and (**II**) in the oxidation of α-tocopherol **1**.

Entry	Catalyst	Conversion [%]			
		Run no. 1[a]	Run no. 2	Run no. 3	Run no. 4
1	PVP-2/MTO (**I**)	60 (53)[b]	61 (49)	59 (48)	60 (49)
2	PVP-25/MTO (**II**)	69 (67)[b]	65 (60)	64 (58)	64 (58)

[a] After the first reaction, catalyst was recovered by filtration; following runs were performed working under the same experimental conditions.
[b] Yields of quinone **2** are given in parentheses.

Table 4. Oxidation of 6-*O*-acetyl-α-tocopherol **4**.



4 **2**

Entry	Catalyst	Conversion [%]	Yield[a] [%]
1	MTO	45	42
3	MTO/L[b]	20	17
4	PVP2/MTO (**I**)	18	16
5	PVP25/MTO (**II**)	40	38
6	PVPN2/MTO (**III**)	15	12
7	PVPN25/MTO (**IV**)	30	26
8	PS/MTO (**V**)	16	15
9	PS/MTO/L (**VI**)[b]	18	17

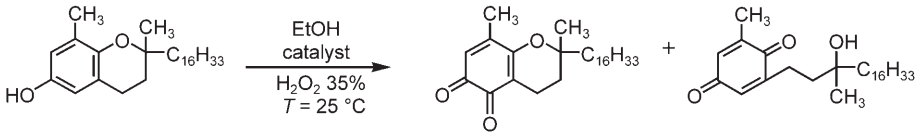
[a] Yield of **2** calculated after 10 h.
[b] L = 2-aminomethylpyridine.

electron-releasing methoxy group at C-6 (numbering of carbon atoms as in Figure 1) improved the conversion of **3** with respect to **1**, still affording the *p*α-TQ **2** in moderate yield (Table 3). These data are in accordance with both the electrophilic character of activated peroxo-rhenium complexes (**A**) and (**B**) and with the electron-releasing property of the methoxy group. Moreover, an appreciable increase of reactivity of microencapsulated catalysts (**V**–**VI**) was observed compared to the oxidation of α-T **1** (Table 3, entries 7 and 8 *vs.* Table 1, entries 3–6), compounds (**II**), (**IV**) and (**VI**) being the most efficient catalysts (Table 1). The oxidation of **3** was repeated with the most reactive catalyst, compound (**II**), to afford a quantitative conversion of the substrate giving **2** in 81% yield (Table 3, entry 9).

Irrespective of the experimental conditions, low values of conversion of substrate were observed in the oxidation of *O*Ac-α-T **4**, presumably due to the electron-withdrawing properties of the acetyl group (Table 4). In this latter case, the *p*α-TQ **2** was obtained as the only recovered product; the yield of **2** increasing with the increase in the value of the reticulation grade of the support (Table 4, entries 4 and 6 *vs.* 3 and 5).

Our attention was next turned to study the oxidation of δ-tocopherylquinone **5** (δ-T **5**). The results of the oxidations are reported in Table 5. Treatment of δ-T **5** with the MTO/H_2O_2 system gave a mixture of *ortho*-δ-tocopherylquinone **6** (δ-tocored; *o*δ-TQ) and *para*-δ-tocopherylquinone **7** (*p*δ-TQ) in low total yield, the *o*δ-TQ being isolated in the major amount after chromatographic purification (Table 5, entry 1). Quinones **6** and **7** were found to be mainly concentrated as an oily red phase, partially soluble in EtOH. The high value of conversion of the substrate and the low mass-balance observed during the oxidation of **5** with MTO suggest the formation of highly degraded, water-soluble and ring-opened derivatives. A similar result was obtained in the oxidation of **5** with the MTO/H_2O_2 system in the most activating AcOH as reaction solvent (Table 5, entry 2). It is noteworthy that the oxidation of **5** with heterogeneous catalysts

Table 5. Oxidation of δ-tocopherol **5**.



5 **6** **7**

Entry	Catalyst	Solvent	Oxidant	Conversion [%]	Product(s)	Yield(s)[a] [%]	Ratio **6**:**7**
1	MTO	EtOH	H_2O_2	>95	**6** (**7**)	21 (9)	2.3:1.0
2	MTO	AcOH	H_2O_2	>95	**6** (**7**)	21 (23)	1.0:1.0
3	MTO/L[b]	EtOH	H_2O_2	96	**6** (**7**)	29 (58)	1.0:2.0
4	PVP2/MTO (**I**)	EtOH	H_2O_2	41	**6** (**7**)	15 (20)	1.0:1.3
5	PVP25/MTO (**II**)	EtOH	H_2O_2	61	**6** (**7**)	23 (27)	1.0:1.2
6	PVPN2/MTO (**III**)	EtOH	H_2O_2	52	**6** (**7**)	21 (17)	1.3:1.0
7	PVPN25/MTO (**IV**)	EtOH	H_2O_2	35	**6** (**7**)	18 (13)	1.4:1.0
8	PS/MTO (**V**)	EtOH	H_2O_2	85	**6** (**7**)	30 (37)	1.0:1.2
9	PS/MTO/L (**VI**)[b]	EtOH	H_2O_2	95	**6** (**7**)	31 (58)	1.0:1.8
10	MTO	CH_2Cl_2	UHP	70	**6** (**7**)	38 (26)	1.5:1.0
11	PVPN2/MTO (**III**)	CH_2Cl_2	UHP	28	**6** (**7**)	16 (11)	1.5:1.0

[a] Yield of **6** and **7** calculated after 10 h.
[b] L = 2-aminomethylpyridine.

(**I**-.**VI**) gave quinones **6** and **7** in moderate to high yields, besides the substrate (Table 5, entries 4–9). The high value of the mass-balance observed under heterogeneous conditions further suggests that the reactivity and selectivity of MTO might be finely tuned by the properties of the polymeric support. To the best of our knowledge this is the first procedure reported for the preparation of *p*δ-TQ **7**.[38] Concerning the selectivity of the oxidation, a different selectivity (expressed as ratio between quinones **6** and **7**) was observed depending on the oxidation state of the nitrogen atom anchorage site for the rhenium atom. In particular, while the *p*δ-TQ **7** was synthesized in highest yield with catalysts (**I**) and (**II**), the *o*δ-TQ **6** became the major reaction product with the corresponding *N*-oxide derivatives (**III**) and (**IV**) (Table 5, entries 4 and 5 *vs.* 6 and 7). As a general trend, microencapsulated catalysts (**V**) and (**VI**) were more reactive than poly(4-vinylpyridine)-based systems, affording **7** as the main reaction product in acceptable yield (Table 5, entries 8 and 9 *vs.* 4–7). The homogeneous complex MTO/L behaves in a way similar to (**VI**), thus confirming that the microencapsulation process did not interfere with the reactivity and selectivity of MTO (Table 5, entry 3 *vs.* 9).

In an effort to evaluate the effect of the primary oxidant on the oxidation of tocopherols, compound **5** was successively oxidized with MTO and (**IV**), using the urea/hydrogen peroxide adduct (UHP) as oxygen atom donor (Table 5, entries 10 and 11). The UHP, in connection with CH_2Cl_2, is widely used in the MTO chemistry to provide an anhydrous reaction medium able to tune the acidity of the system by release of the basic urea during the consumption of H_2O_2.[39] While the MTO/UHP system was more selective than MTO/H_2O_2 (Table 5, entry 10 *vs.* 1), catalyst (**V**) showed a similar performance irrespective of the nature of the primary oxidant (Table 5, entry 11 *vs.* 7). For this reason the successive transformations were performed with the less expensive and easily available H_2O_2. Table 6 shows that, in a selected case, catalyst (**III**), poly(4-vinylpyridine) systems are stable enough to perform at least four recycling experiments of the oxidation of **5** with similar conversion of substrate and yield of products. The covalent adducts of the δ-tocopheroxyl radical with the alkylperoxyl radical and some other products of radical polymerization have been reported to be formed during the oxidation of δ-T **5** with peroxyl radical generated from 2,2′-azobis(2,4-dimethylvaleronitrile) (AMVN).[40] However, these products were not recovered in the reaction mixture of **5** with supported MTO catalysts as a consequence of a concerted mechanism.

Concerning the effect of substituents with different electronic properties on the oxidation of **5**, the presence of the electron-releasing methoxy group on C-6, as in the case of 6-*O*-methyl-δ-tocopherol **8**, generally improved the conversion of substrate, quinones **6** and **7** being isolated in moderate yields (Table 7, entries 1–8). Noteworthy, irrespective of the experimental conditions, the *p*δ-TQ **7** was obtained as the main reaction product. The oxidation of **8** with heterogeneous catalysts (**I**–**VI**) showed a value of mass-balance higher than that observed with MTO alone (Table 7, entries 3–8 *vs.* 1). These data are in accordance with data previously observed for the parent compound δ-T **5**. Compound **7** was recovered with microencapsulated catalysts (**V**–**VI**) in a yield higher than that obtained with poly(4-vinylpyridine) based systems, catalyst **VI** being the best catalyst system (Table 7, entry 8) Again, catalyst **VI** showed a behaviour similar to that of its parent homogeneous complex MTO/L (Table 7, entry 8 *vs.* 2). The oxidation of **8** was repeated with the most reactive catalyst, compound (**II**), to afford quantitative conversion of the substrate giving **6** and **7** in 42 and 45% yields, respectively (Table 7, entry 9). Treatment of 6-*O*-acetyl-δ-tocopherol **9** (not shown) with two selected catalysts, MTO and compound (**I**), was not effective, and only substrate was recovered at the end of the reaction. These results, compared with that previously obtained in the oxidation of 6-*O*-acetyl-α-tocopherol, clearly suggest that the number of electron-releasing methyl groups on the aromatic ring is a crucial factor for the oxidation of electron-poor tocopherols.

Finally, we studied the oxidation of γ-tocopherol **10** (γ-T) under similar experimental conditions. The results of the oxidations are reported in Table 8. Treatment of the γ-T **10** with the MTO/H_2O_2 system gave a mixture of *ortho*-γ-tocopherylquinone **11** (γ-tocored; *o*γ-TQ) and *para*-γ-tocopherylquinone **12** (*p*γ-TQ) in both low yield and mass-balance with respect to converted substrate, compound **12** being the major reaction product (Table 8, entry 1). A better result was

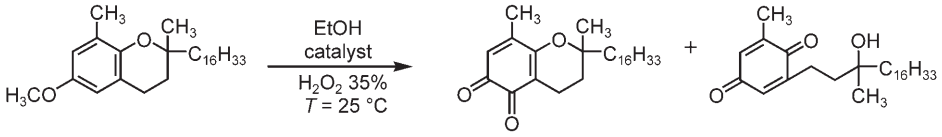
Table 6. Stability of catalyst (**III**) in the oxidation of δ-tocopherol **5**.

Entry	Catalyst	Conversion (%)			
		Run no. 1[a]	Run no. 2	Run no. 3	Run no. 4
1	PVPN2/MTO (**III**)	52 [21 (17)][b]	50 [23 (15)]	48 [21 (13)]	49 [20 (16)]

[a] After the first reaction, catalyst was recovered by filtration; following runs were performed working under the same experimental conditions.

[b] Yields of *ortho*-quinone **6** and *para*-quinone **7**, respectively, are given in parentheses.

Table 7. Oxidation of 6-*O*-methyl-δ-tocopherol **8**.

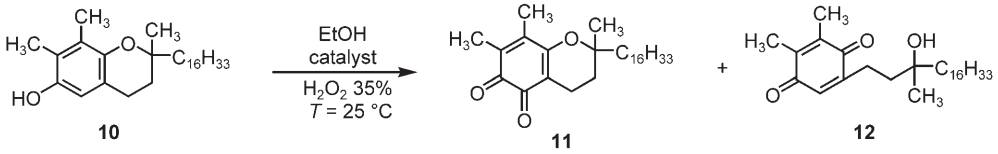


8 **6** **7**

Entry	Catalyst	Conversion [%]	Product(s)	Yield(s)[a] [%]	Ratio **6**:**7**
1	MTO	>95	**6** (**7**)	15 (23)	2.3:1.0
2	MTO/L[b]	60	**6** (**7**)	14 (35)	1.0:2.5
3	PVP2/MTO (**I**)	66	**6** (**7**)	22 (38)	1.0:1.7
4	PVP25/MTO (**II**)	50	**6** (**7**)	19 (28)	1.6:1.0
5	PVPN2/MTO (**III**)	75	**6** (**7**)	32 (36)	1.0:1.1
6	PVPN25/MTO (**IV**)	70	**6** (**7**)	26 (35)	1.0:1.4
7	PS/MTO (**V**)	49	**6** (**7**)	11 (30)	1.0:2.8
8	PS/MTO/L (**VI**)[b]	61	**6** (**7**)	13 (40)	1.0:3.0
9	PVP25/MTO (**II**)	>95	**6** (**7**)	42 (45)[c]	1.0:1.1

[a] Yield of **6** and **7** calculated after 10 h.
[b] L = 2-aminomethylpyridine.
[c] Yield of **6** and **7** calculated after 48 h.

Table 8. Oxidation of γ-tocopherol **10**.



10 **11** **12**

Entry	Catalyst	Conversion [%]	Product(s)	Yield(s)[a] [%]	Ratio **11**:**12**
1	MTO	>90	**11** (**12**)	17 (29)	1.0:1.7
2	MTO/L[b]	15	**11** (**12**)	8 (7)	1.0:1.0
3	PVP2/MTO (**I**)	58	**11** (**12**)	22 (10)	2.1:1.0
4	PVP25/MTO (**II**)	74	**11** (**12**)	29 (39)	1.0:1.4
5	PVPN2/MTO (**III**)	42	**11** (**12**)	12 (10)	1.3:1.0
6	PVPN25/MTO (**IV**)	56	**11** (**12**)	27 (14)	1.9:1.0
7	PS/MTO (**V**)	58	**11** (**12**)	26 (20)	1.3:1.0
8	PS/MTO/L (**VI**)[b]	25	**11** (**12**)	12 (9)	1.3:1.0

[a] Yield of **11** and **12** calculated after 10 h.
[b] L = 2-aminomethylpyridine.

obtained with heterogeneous catalysts (**I**–**VI**), in which cases the highest yield of quinones **11** and **12** was generally observed (Table 8, entries 3–8 *vs.* 1).

In the family of poly(4-vinylpyridine) catalysts the reactivity increased with increasing reticulation grade of the polymer, while it was found to be decreased by changing the oxidation state of the pyridinyl moiety (Table 8, entries 4 and 6 *vs.* 3 and 5), catalyst (**IV**) affording the highest yield of *o*γ-TQ **11**. A different behaviour was observed with microencapsulated catalysts (**V**–**VI**), in which case the *p*γ-TQ 12 was isolated as the main reaction product in moderate yield (Table 8, entries 7 and 8 *vs.* 3–6). Moreover, catalyst (**VI**) and its parent homogeneous complex MTO/L showed a poor reactivity (Table 8, entries 2 and 8).

Noteworthy, the oxidation of γ-T **9**, performed under radical conditions (AMVN), afforded *o*γ-TQ **11**, alkylperoxy-γ-tocopherones and γ-tocopherol dimers as the only recovered products.[41] More stringent experimental conditions only afforded an extensive degradation of the products. Recently, among the wide panel of biological activities reported for tocopherols, particular attention has been focused on the possibility to use vitamin E as a nutritional supplement to antagonize the major pathogenic processes of influenza A in humans, mainly in connection with the high level of attention of the World Health Organization for human cases of avian H5N1 influenza. Every year, influenza epidemics cause numerous deaths and millions of hospitalizations, but the most frightening

effects are seen when new strains of the virus emerge, causing world-wide outbreaks of infection. Influenza virus is an enveloped virus with segmented, single-stranded, negative-sense RNA genomes.[42] Several antiviral compounds have been developed against influenza virus, but their long-term efficacy is often limited by toxicity and the almost inevitable selection of drug-resistant viral mutants. Numerous antioxidant substances are able to inhibit the replication of different types of viruses both *in vivo* and *in vitro*.[43] In particular, a significant body of medical and scientific evidence exists to suggest that vitamin E may show appreciable effects in the protection of lungs and other vital organs from virus replication and cytokine-induced oxidative stress, due to its antioxidant property.[44] On the other hand, the *in vivo* biological activity of vitamin E strictly depends on the production of the corresponding tocopherylquinones by cytochrome P450-dependent enzymes. In fact, quinones can act as potent electrophiles modifying the internal redox potential of the cell.[43] Because of the lack of data on the anti-influenza activity of single tocopherols and tocopherylquinones, we studied the antiviral activity of α-T **1**, *p*α-TQ **2**, 6-*O*-methyl-α-tocopherol **3**, 6-*O*-acetyl-α-tocopherol **4**, δ-T **5**, *p*δ-TQ **7**, 6-*O*-methyl-δ-tocopherol **8**, 6-*O*-acetyl-δ-tocopherol **9**, γ-T **10**, *p*γ-TQ **12**, as a representative panel of tocopherol derivatives, against influenza virus A. To test viral production, supernatants from infected MDCK cells (see Experimental Section) were harvested at different time points after virus challenge and were tested by measuring the hemagglutinin units (HAU).[45] As shown in Table 9, all the reduced forms of tocopherols (**1**, **3**, **4**, **5**, **8**, **9**, **10**) were able to inhibit influenza virus in a dose-dependent manner. In particular, these compounds presented an ED_{50} (the inhibitory concentration required to reduce virus yield by 50%) ranging from 292.6 (5) and 549.2 (3) μM. On the contrary, the product of δ-T (7) oxidation showed a partial antiviral efficacy only when administered at the higher dose. Moreover, the products of α-T (2) and γ-T (12) oxidation were not able to inhibit viral replication, indicating that the oxidized forms of tocopherols lose the antiviral activity against influenza virus (Table 9).

Table 9. Antiviral activity against influenza virus of tocopherol components and derivatives.

Compound	ED_{50} [μM][a]
α-T (**1**)	424
*p*α-TQ (**2**)	n.d.
6-*O*-methyl-α-tocopherol (**3**)	549.2
6-*O*-acetyl-α-tocopherol (**4**)	338.6
δ-T (**5**)	292.6
*p*δ-TQ (**7**)	>500
6-*O*-methyl-δ-tocopherol (**8**)	511.8
6-*O*-acetyl-δ-tocopherol (**9**)	511.8
γ-T (**10**)	329.4
*p*γ-TQ (**12**)	n.d.

[a] ED_{50} = inhibitory concentration required to reduce virus yield by 50%. The results are the mean values of two independent determinations.

Cell morphology and viability were unaffected by treatment with all the tested compounds, which tends to exclude the possibility that the reduction in viral replication was due to cytotoxic effects of their inhibitors.

Conclusions

Supported MTO catalysts (**I–VI**) were efficient and selective systems for the oxidation of tocopherols to the corresponding *ortho*- and *para*-tocopherylquinones in moderate to high yield, under environmentally friendly conditions and employing simple work-up procedures. It is worth noting that these oxidations occur at room temperature in ethanol, thus avoiding the use of chlorinated organic solvents or AcOH as are often used in MTO-catalyzed oxidations of aromatic derivatives. In some cases, the *para*-tocopherylquinones were synthesized for the first time. Presumably, the high catalyst activity observed for the heterogeneous MTO systems might be ascribed to the formation of MTO reactive monoperoxo $[MeRe(O)_2O_2]$ (**A**) and bis-peroxo $[MeReO(O_2)_2]$ (**B**) η^2-rhenium complexes. The reticulation grade of the polymer and the oxidation state of the site of anchorage for the rhenium atom on the polymer appear to be crucial variables for the reactivity of poly(4-vinylpyridine) and poly(4-vinylpyridine *N*-oxide)/MTO catalysts. Polymer-supported MTO systems (**I–III**) were stable enough to perform at least four recycling experiments with similar conversion and selectivity. As a general trend, MTO was more reactive than polymer-supported MTO catalysts, probably due to the presence of a kinetic barrier of the substrate to approach the supported rhenium complexes. On the other hand, the oxidations performed with MTO were less selective than that performed under heterogeneous conditions, as shown by the low values of the mass-balance of the reaction. Concerning the selectivity of the reaction (that is *ortho*- versus *para*-tocopherylquinone), with the exception of the oxidation of α-T, in which case only the corresponding *p*α-TQ was obtained, a generalized trend cannot be drawn, in the sense that none of the catalysts performs uniformly best with all the substrates. However, optimized conditions can be identified for each substrate, which allow us to enhance considerably the selectivity. For example, the highest yield of *p*δ-TQ was obtained with catalyst (**VI**), while *o*δ-TQ predominated with catalyst (**IV**). Analogously, the *p*γ-TQ was recovered in highest yield with catalyst (**III**) and the corresponding isomer

*o*γ-TQ with catalyst (**VI**). On the basis of the biological assay, the activity of tocopherols against influenza virus is higher than that showed by the corresponding tocopherylquinones, thus suggesting, for the first time, a drawback effect of the oxidative metabolism on the antiviral activity of these compounds.

Experimental Section

General Remarks

The α-tocopherol **1**, γ-tocopherol **5**, δ-tocopherol **9**, hydrogen peroxide (35% water solution), methylrhenium trioxide (MTO), 2-methylaminopyridine, poly(4-vinylpyridine) 2% and 25% cross-linked with divinylbenzene, polystyrene 2% cross-linked with divinylbenzene, and analytical reagent grade organic solvents were purchased (Aldrich) and used without any further purification. The 6-*O*-methyl-α-tocopherol **3**, 6-*O*-acetyl-α-tocopherol **4** and 6-*O*-methyl-δ-tocopherol **8** were prepared according to literature methods.[46] Chromatographic purifications were performed on columns packed with silica gel, 230–400 mesh, for the flash technique. NMR spectra were recorded in $CDCl_3$ on a Bruker spectrometer (200 MHz) and are reported in δ (ppm) value.

Cell Cultures

Madin–Darby canine kidney (MDCK) cells were grown in RPMI 1640 medium supplemented with 10% fetal calf serum (FCS); glutamine 0.3 mg mL^{-1}; penicillin 100 U mL^{-1}; and streptomycin 100 mg mL^{-1}. Cell viability was estimated by trypan blue (0.02%) exclusion. All reagents were purchased from Invitrogen (Milan, Italy).

Virus Production, Infection, and Titration

Influenza virus A/Puerto Rico/8/34 H1N1 (PR8 virus) was grown in the allantoic cavities of 10 day-old embryonated chicken eggs. After 48 h at 37 °C, the allantoic fluid was harvested and centrifuged at 5000 rpm for 30 min to remove cellular debris. The titer of virus preparation was 3.5×10^7 plaque-forming units (p.f.u.) mL^{-1}. Confluent monolayers were challenged for 1 h at 37 °C with PR8 at a multiplicity of infection (m.o.i.) of 0.05, incubated for 1 h at 37 °C, washed with PBS, and then incubated with medium supplemented with 2% FCS. Mock infection was performed with the same dilution of allantoic fluid from uninfected eggs. Virus production was determined in the supernatants of infected cells at different times post infection (p.i.), by measuring the hemagglutinin units (HAU), using human type 0 Rh^+ erythrocytes. For the evaluation of antiviral activity, the compounds were diluted in RPMI and added at the appropriate dilution after the adsorption period and maintained in the culture media until the end of the experiments.

Preparation of Heterogeneous MTO Catalysts (I–V)

Poly(4-vinylpyridine)/MTO (PVP2/MTO **I**, PVP25/MTO **II**), poly(4-vinylpyridine *N*-oxide)/MTO (PVPN2/MTO **III**, PVPN25/MTO **VI**,) and polystyrene/MTO (PS/MTO **V**) catalysts were prepared as previously reported.[25a] In summary, MTO [25 mg (0.1 mmol) or 13 mg (0.05 mmol)] was added to a suspension of the appropriate resin (100 mg) in ethanol (4 mL), or tetrahydrofuran in the case of polystyrene. The mixture was stirred for 1 h using a magnetic stirrer. Coacervates were found to envelop the solid core dispersed in the medium and hexane (5 mL) was added to harden the capsule walls. The solvent was removed by filtration, and the solid residue was washed with ethyl acetate and finally dried under high vacuum. In every case, MTO was completely included into the polymer. This result was confirmed by spectroscopic analysis of the residue obtained after evaporation of the organic layers. The catalysts were used without any further purification.

Oxidation of Tocopherols and Tocopherol Derivatives: General Procedures

Homogeneous oxidation: A 5-mL reaction flask was charged sequentially with MTO (0.01 mmol), 1 mL ethanol and H_2O_2 (35% aqueous solution). The stirred solution became yellow due to the formation of peroxo species and after that a solution of the tocopherol (0.5 mmol) in ethanol (1 mL) was added. The mixture was stirred at room temperature until no more starting material could be detected on TLC. It was then diluted with both EtOAc (50 mL) and water (3 mL) and the excess of hydrogen peroxide was decomposed by addition of a little MnO_2. After filtration, the organic layer was washed with brine (2×10 mL) and dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The products were obtained by chromatographic purification in acceptable to good yields and identified by spectroscopic analyses and comparison with authentic samples.

Heterogeneous oxidation: To the solution/suspension of the tocopherol (1.0 mmol) in EtOH (2 mL) were added the appropriate heterogeneous catalyst (0.01 mmol of MTO, loading factor 1.0 mmol $g)^{-1}$ and H_2O_2 (35% aqueous solution, amount indicated in the Tables) as primary oxidant the mixture was stirred ay room temperature until no more starting material could be detected on TLC. The suspension was filtered off, and the recovered catalysts washed with ethyl acetate. After drying under high vacuum, some of the catalysts were used for further reactions to evaluate their stability. The organic solution was dried over Na_2SO_4 and the solvent removed under reduced pressure.

***para*-α-Tocopherylquinone 2** (ref.[47]): UV: $\lambda_{max} = 276$ nm; ^{1}H NMR: $\delta = 2.5$ (t, 2H, $J = 8.5$ Hz, CH_2), 1.9 (m, 2H, CH_2), 1.96 (s, 9H, $3CH_3$), 1.5–1.0 (m, 21H, 3CH, $9CH_2$), 1.3 (s, 3H, CH_3), 0.83 (s, 6H, $2CH_3$), 0.78 (s, 6H, $2CH_3$); ^{13}C NMR: $\delta = 188.45$ (C=O), 187.30 (C=O), 144.50 (C), 140.44 (C), 140.20 (C), 140.10 (C), 72.58 (C-OH), 42.23 (CH_2), 40.16 (CH_2), 39.31 (CH_2), 37.66 (CH_2), 37.57 (CH_2), 37.33 (CH_2), 37.22 (CH_2), 32.71 (CH), 27.89 (CH), 26.51 (CH), 24.73 (CH_3), 24.42 (CH_2), 22.64 (CH_2), 22.55 (CH_3), 21.36 (CH_3), 21.27 (CH_2), 20.93 (CH_3), 19.67 (CH_2), 19.60 (CH_3), 14.11 (CH_3), 12.27 (CH_3), 12.19 (CH_3).

***ortho*-δ-Tocopherylquinone 6** (ref.[40a]): UV: $\lambda_{max} = 276.5$ nm; ^{1}H NMR ($CDCl_3$): $\delta = 6.13$ (s, 1H, CH), 2.43 (m, 2H, CH_2), 2.08 (s, 3H, CH_3), 1.71 (m, 2H), 1.6–0.9 (broad m, 21H), 0.83 (m, 12H); ^{13}C NMR ($CDCl_3$): $\delta = 180.7$ (C=O), 177.9 (C=O), 162.1 (C), 150.2 (C), 126.6 (CH), 112.2 (C), 87.9 (CH), 41.0 (CH_2), 39.5 (CH_2), 39.4 (CH_2), 37.3 (2×

CH_2), 37.3 ($2\times CH_2$), 32.8 (CH), 32.6 (CH), 29.5 (CH), 28.0 (CH_2), 24.8 (CH_3), 24.4 (CH_2), 23.8 (CH_2), 23.7 (CH_2), 22.7 (CH_3), 22.6 (CH_3), 20.9 (CH_3), 19.8 (CH_3), 19.6 (CH_3); MS: $m/z=416$ (M^+, 72%).

***para*-δ-Tocopherylquinone 7:** UV: $\lambda_{max}=276.5$ nm; ^{1}H NMR ($CDCl_3$): $\delta=6.64$ (m, 1H, CH), 6.60 (m, 1H, CH), 2.30 (m, 2H, CH_2), 2.07 (s, 3H, CH_3), 1.50 (m, 2H), 1.4–0.9 (broad m, 21H), 0.83 (m, 12H); ^{13}C NMR ($CDCl_3$): $\delta=$ 185.5 (C=O), 185.0 (C=O), 148.2 (C), 145.7 (C), 133.6 (CH), 128.1 (CH), 72.5 (C), 42.2 (CH_2), 39.5 (CH_2), 39.4 (CH_2), 37.5 ($2\times CH_2$), 37.2 ($2\times CH_2$), 32.8 (CH), 32.7 (CH), 29.7 (CH), 27.9 (CH_2), 26.6 (CH_3), 24.8 (CH_2), 23.8 (CH_2), 23.7 (CH_2), 22.7 (CH_3), 21.1 (CH_3), 19.6 (CH_3), 16.3 (CH_3), 16.0 (CH_3); MS: $m/z=416$ (M^+, 72%).

***para*-γ-Tocopherylquinone 6:** ^{1}H NMR ($CDCl_3$): $\delta=6.51$ (s, 1H, CH), 2.50 (t, 2H, $J=7.6$ Hz, CH_2), 2.0 (s, 6H, $2CH_3$), 1.98 (m, 2H, CH_2), 1.5–1.0 (broad m, 21H), 1.2 (s, 3H, CH_3), 0.85 (s, 6H, $2CH_3$), 0.8 (s, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$): $\delta=184.0$ (C=O), 170.9 (C=O), 149.4 (C), 141.5 (C), 140.6 (C), 132.1 (CH), 72.4 (CH), 42.1 (CH_2), 39.5 (CH_2), 37.9 (CH_2), 37.9 (CH_2), 37.8 (CH_2), 37.6 (CH_2), 35.9 (CH_2), 33.1 (CH), 33.0 (CH), 28.0 (CH), 26.7 (CH_3), 25.2 (CH_2), 25.2 (CH_2), 24.8 (CH_2), 22.7 (CH_3), 22.6 (CH_3), 20.8 (CH_2), 20.3 (CH_3), 19.9 (CH_3), 12.2 (CH_3), 11.6 (CH_3); MS: $m/z=430$ (M^+, 71%).

***ortho*-γ-Tocopherylquinone 7** (ref.[48]): UV: $\lambda_{max}=281$ nm; ^{1}H NMR ($CDCl_3$): $\delta=2.41$ (q, 2H, $J=7$ Hz, CH_2), 2.03 (s, 3H, CH_3), 1.95 (s, 3H, CH_3), 1.73 (q, 2H, $J=6.8$ Hz, CH_2), 1.32 (s, 3H, CH_3), 1.09–1.67 (broad m, 21H), 0.83–0.88 (m, 12H); ^{13}C NMR ($CDCl_3$): $\delta=180.8$ (C=O), 179.8 (C=O), 163.2 (C), 143.6 (C), 134.2 (C), 110.3 (C), 81.4 (C), 40.0 (CH_2), 37.4 ($2\times CH_2$), 37.3 ($2\times CH_2$), 32.8 (CH), 32.6 (CH), 30.0 (CH_2), 28.0 (CH), 24.8 (CH_2), 24.4 (CH_2), 23.9 (CH_3), 22.7 (CH_3), 22.6 (CH_3), 20.9 (CH_2), 19.7 (CH_3), 19.6 (CH_3), 15.4 (CH_2), 13.7 (CH_3), 12.2 (CH_3); MS: $m/z=430$ (M^+, 72%).

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