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Patel, Anjan; Rosenau, Thomas

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ORIGINAL PAPER

Synthesis and analytical characterization of *N*-methylated derivatives of α-tocopheramine and their oxidation products

Anjan Patel[1] · **Thomas Rosenau**[1,2]

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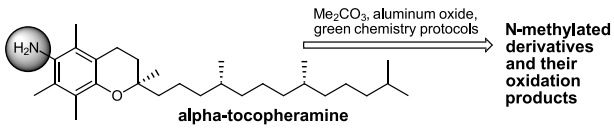
Abstract

N-Methylated derivatives of α-tocopheramine, which have preliminarily been shown to have good performance as stabilizers of cellulose solutions in ionic liquids for production of cellulosic manmade fibers, have not been accessible in sufficient amounts by green syntheses. In this study, the *N*-methyl-, *N*,*N*-dimethyl-, and *N*,*N*,*N*-trimethylammonium derivatives of α-tocopheramine were synthesized and fully analytically characterized. The procedures used dimethyl carbonate as solvent and methylating agent as well as aluminum oxide as the reusable catalyst. Care was taken to ensure that the procedures conformed to green chemistry principles and were easily upscalable.

Graphical abstract



Keywords Tocopheramines · Vitamin E · *Ortho*-quinone methide · *N*-Methylation · Oxidation

Introduction

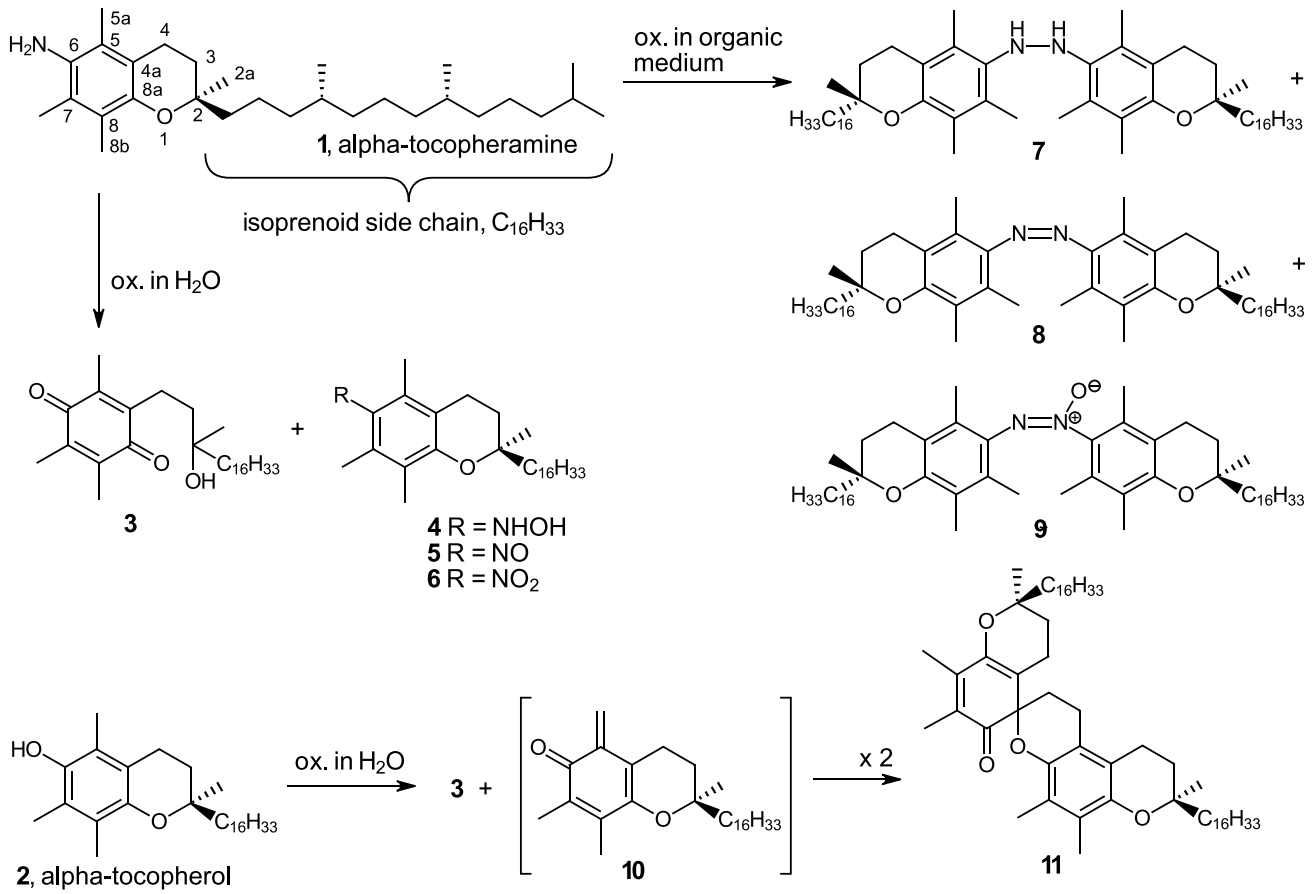
α-Tocopheramine (**1**) has been described as early as 1942. It is distinguished from its more popular brother – α-tocopherol (**2**), the main component in vitamin E by an amino group instead of tocopherol´s phenolic OH group [1, 2]. Tocopheramines are biocompatible [2, 3], have been proposed as food and feed additives [4, 5] and studied for their promising anticancer and proapoptotic activities [6–10]. Similar to tocopherols, which made the move from medical, physiological uses and usage as major food/feed additives to all kinds of technological applications as antioxidants, also tocopheramines have been tested with good success with respect to general uses as antioxidant stabilizers in technical applications, such as surfactants [11], polymer stabilizers [12], and stabilizers for Lyocell spinning dopes and the resulting cellulosic fibers [13, 14]. However, large scale application had been hampered by two facts: first, the limited availability: α-tocopheramine is usually synthesized according to a rather complex multi-step approach which has not yet left lab scale [15]. Second, the nature of the byproducts produced from α-tocopheramine especially with regard to chromophoric degradation products has remained unclear until recently. α-Tocopherol, by contrast, is produced on a large industrial scale and its oxidation chemistry and reaction products in all kinds of different setups and reaction systems have been extensively described [16, 17]. At least the obstacle of unknown degradation products has been removed recently, with the structural elucidation and analytical characterization of all monomeric *N*-oxidation [18] and dimeric N–N coupling products of α-tocopheramine [19]. It can also be expected that the problem of limited availability will be tackled with new vigor as recent results have shown tocopheramines to be excellent stabilizers for cellulosic fiber

✉ Thomas Rosenau
thomas.rosenau@boku.ac.at

[1] Institute of Chemistry of Renewable Resources, Department of Chemistry, University of Natural Resources and Life Sciences (BOKU), Muthgasse 18, 1190 Vienna, Austria

[2] Faculty of Science and Engineering, Laboratory of Natural Materials Technology, Åbo Akademi University, Porthansgatan 3, 20500 Åbo, Turku, Finland

Scheme 1



spinning from ionic liquid solutions [13] which should result in much greater demand to be met.

α-Tocopherylquinone (**3**) [17, 20] is the main product of the oxidation of α-tocopheramine under aqueous conditions or in the presence of water, accompanied by small amounts of monomeric *N*-oxidized derivatives (**4**–**6**), usually around 2–5% (Scheme 1). Under non-aqueous conditions, dimeric, N,N-coupled oxidation products, namely *N*,*N*-bis(tocopheryl)hydrazine (**7**), azo-tocopherol (**8**), and azoxytocopherol (**9**), dominate [21–25] and no tocopherylquinone (**3**) is formed. Compared to α-tocopherol, which forms **3** in aqueous media and the transient 5a-*ortho*-quinone methide intermediate (**10**) [26–28] that dimerizes into the α-tocopherol spiro-dimer (**11**) [29, 30] in organic media (Scheme 1), α-tocopheramine gives rise to a wider spectrum of oxidation products, due to the different possible oxidation and coupling products of its amino function.

Tocopheramine derivatives have recently been employed as stabilizers for cellulose solutions in *N*,*N*-dialkylimidazolium ionic liquids, to hold autoxidation reactions at bay that otherwise would oxidatively damage the polymer, decrease the molecular weight of the celluloses and cause discoloration of the spinning dope and the resulting fibers [13]. Interestingly, the *N*-alkyl-protected derivatives, available only in milligram amounts, performed better than the parent α-tocopheramine, both with regard to the antioxidative effect and with regard to the minimization of chromophoric compounds. This might seem logical insofar as certain UV-active oxidative byproducts, such as the nitroso, nitro, azo, and azoxy derivatives (**5**, **6**, **8**, **9**), can readily be formed starting from of α-tocopheramine itself, but not from *N*-alkylated variants. Unfortunately, the *N*-alkylated derivatives – with the *N*-methylated compounds as the structurally simplest representatives – are not available, nor are synthesis procedures published.

This provided the impetus to the present study: development of a synthetic approach to *N*-methylated tocopheramines and, as reported in follow-up accounts, identification of their oxidation products. As side conditions, the synthesis approach was supposed to employ green chemistry principles as strictly as possible, to be compatible with the sustainable cellulose fiber spinning approaches in which the antioxidants are to be used. It can reasonably be hypothesized that *N*-methylation of the amino function in tocopheramine

derivatives simplifies its oxidation chemistry in a way that the number of possible byproducts is decreased and that these byproducts are less chromophoric compared to α-tocopheramine (**1**). In this study, we consequently report the synthesis of the *N*-methyl, *N*,*N*-dimethyl, and *N*,*N*,*N*-trimethylammonium derivative of α-tocopheramine (**1**) in facile one-pot, multigram approaches, along with their comprehensive analytical data.

Results and discussion

α-Tocopheramine (**1**) was the obvious starting material for our synthesis attempts. While chemical literature is full of procedures to methylate or permethylate amines, most *N*-alkylation approaches employ methyl halides, and reduction procedures use the (para)formaldehyde / formic acid couple (Leuckart–Wallach type reactions) [31, 32]. Both options seemed less optimal to us from the viewpoint of sustainable chemistry. Nevertheless, we tested different methylations with methyl iodide, and the variant in acetone in the presence of pulverized anhydrous K_2CO_3 worked best, giving convincing yields of 82%. Apparently, the initially formed *N*-methyl-α-tocopheramine (**12**) was a better nucleophile than the starting amine **1**, because even with a 1.4-fold molar excess of alkylating agent, some starting amine remained unmethylated. With a 1.5-fold molar excess, the starting amine was completely consumed, but half of the starting amine was converted to the *N*,*N*-dialkylated product *N*,*N*-dimethyl-α-tocopheramine (**13**) besides the targeted *N*-monomethylated **12**, so that chromatographic purification was required (46% and 49%, respectively). The alternative Leuckart–Wallach approaches provided always a mixture of mono- and demethylated products when using less than 2.5 molar HCHO-equivalents. Even at small ratios of HCHO and amine of 0.5 and below, the tertiary amine (dimethylated product) dominated over the secondary (monomethylated) one: at a HCHO/**1** ratio of 0.3 and 0.5, the ratio between **12** and **13** was 1:2.4 and 1:2.8, respectively. At a molar HCHO/**1** ratio larger than 2.5, yields of **13** were convincingly high (92%), slightly reduced only by a chromatographic purification step that turned out to be necessary to remove the dark brown discoloration of the crude product.

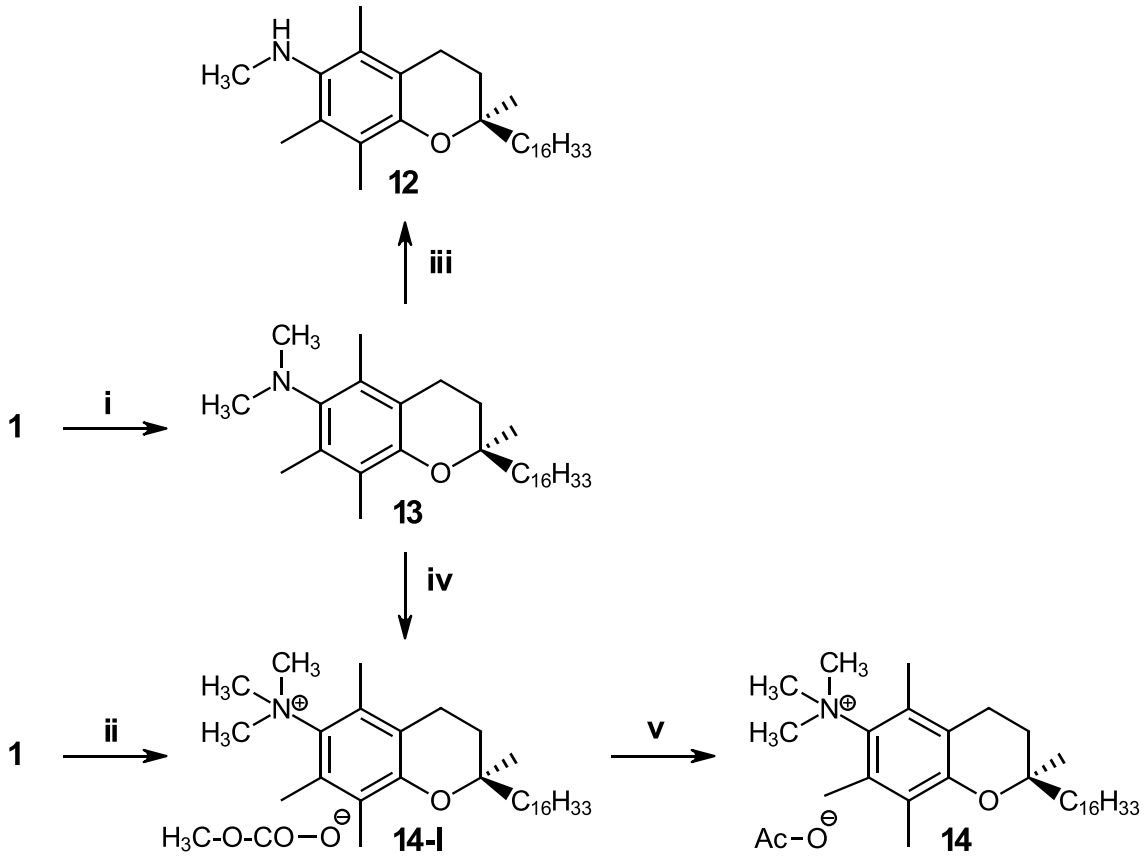
The major objection against these two approaches was the use of the cancerogenic reagents, methyl halide or formaldehyde, which were largely incompatible with our intention to adhere to green chemistry principles. After some additional trials, we resorted to a procedure that used dimethyl carbonate, one of the recommended sustainable and very cheap solvents, as the methylating agent. Under appropriate conditions, i.e., in the absence of water and the presence of a basic catalyst, dimethyl carbonate is able to methylate amino groups in excellent yields and in a "traceless" manner, generating only water, CO_2 and some methanol as the byproducts. In our previous studies, dimethyl carbonate had been used in this way for methylation of amino functions, in the synthesis of isotopically labeled variants of the cellulose solvents *N*,*N*-dimethylacetamide, *N*-methylmorpholine-*N*-oxide and 1-alkyl-3-methylimidazolium acetate [33, 34].

Based on these experiences, we used dimethyl carbonate as solvent and reagent, in combination with aluminum oxide (alox) as a water trap and catalyst. Being used most commonly as bulk stationary phase for chromatography similar to silica gel, aluminum oxide is non-toxic, cost-effective, easy to remove by filtration, recyclable by calcination, and very effective at adsorbing polymeric and chromophoric byproducts. It is commercially available in different degrees of hydration (Brockmann grades I–V) and has either Lewis-acidic or Lewis-basic character; neutral alox is actually a mixture of both variants.

The reaction setup for the methylation was intriguingly simple, the conversion proceeds in a pressure reactor (autoclave) under stirring, in the presence of excess dimethyl carbonate in which aluminum oxide is suspended. From the optimization experiments, it was evident that a higher hydration state (larger Brockmann numbers) was detrimental: the yield dropped to 35% when using grade II instead of grade I, and down to 8% for Brockmann grade III. Interestingly, basic aluminum oxide gave rise to the tertiary amine only, not even low yields of quaternization products (ammonium salts) were formed. With acidic alox, by contrast, only the quaternary ammonium salt was produced, and no non-quaternized amines remained. This offered a very convenient way to switch between permethylation to the tertiary amine and quaternization to the ammonium salt simply by using another type of aluminum oxide as the solid catalyst.

Using the reaction conditions of previous work (350 °C for 3 h), we observed complete consumption of the starting tocopheramine (**1**) in the presence of basic alox, a yield of 72% of the targeted *N*,*N*-dimethyl-α-tocopheramine (**13**), absence of the quaternized product, and formation of byproducts as black, viscous tar. As higher reaction temperature and longer reaction times promote side reactions, in particular chromophore formation, we tried to reduce temperature and reaction time as much as possible, while in return increasing the amount of alox to keep the conversion complete. The conditions were optimized in a design-of-experiment approach using temperature, reaction time, and mass of catalyst as the influencing factors. The optimized conditions used a temperature as low as 120 °C for 30 min with a fivefold mass of alox (Brockmann grade I, relative to **1**) and 50 cm^3 of dimethyl carbonate up to 5 g of tocopheramine (see Scheme 2). Under these conditions, conversion of **1** stayed complete, but chromophore formation was almost completely suppressed, and the reaction mixture appeared

Scheme 2



i = a) Me_2CO_3 (50 mL / 5 g of **1**), basic Al_2O_3 (Brockmann I, 5 wt. eq.), 120°C, 30 min, b) basic Al_2O_3 (Brockmann I, 5 wt. eq.), r.t., 5 min, 97 %
ii = a) Me_2CO_3 (50 mL / 5 g of **1**), acidic Al_2O_3 (Brockmann I, 5 wt. eq.), 120°C, 30 min, b) active C (0.5 wt. eq.), r.t., 5 min, 91 %
iii = a) Na_2CO_3*H_2O_2, cyrene, r.t., 2 h, b) NHDT/Na_2SO_3, cyrene, r.t., 10 min, 94 %
iv = a) Me_2CO_3 (50 mL / 5 g of **1**), acidic Al_2O_3 (Brockmann I, 5 wt. eq.), 120°C, 30 min, b) active C (0.5 wt. eq.), r.t., 5 min, 97 %
v = HOAc (glacial), 30 min, r.t., vacuum, 91%

only slightly yellow. By adding another five mass-equivalents of alox after cooling the reaction mixture to room temperature, the colored byproducts were completely adsorbed to the solid and were removed together with the solids simply by filtration. No other byproducts were detectable in the colorless filtrate, eliminating any need for chromatographic purification. With 91%, the yield of **13**, a colorless oil, was quite satisfactory.

The yield of **13** can even be increased by another 6% by washing the solid alox remainder with additional solvents. However, even very apolar solvents (*n*-hexane, *n*-heptane, or petroleum ether) eluted not only residual adhering product, but also some of the colored byproducts, so that the minor yield gain would come at the expense of an additional chromatographic purification step with much higher overall solvent usage, which has to be critically considered with regard to economy and sustainability. It should be noted that the absolute amount of chromophores as usual in chromophore chemistry [35] was very low, in the sub-milligram range, which might not seem to be a critical issue. However, as the compounds are to be applied as stabilizers of spinning dopes for cellulose fibers, the starting discoloration should be as low as possible and any intake of chromophores needs to be minimized.

Under otherwise identical reaction conditions, with the only exception of using acidic aluminum oxide (Brockmann grade I) instead of basic one, the starting amine **1** was neatly quaternized to *N*,*N*,*N*-trimethyl-α-tocopherol ammonium,

obtained initially as a mixture of carbonate and methyl carbonate as the counter anions (**14-I**). By dissolving the crude product in acetic acid, trituration with active charcoal and filtration through celite to remove chromophores, and evaporation under reduced pressure, *N*,*N*,*N*-trimethyl-α-tocopherol ammonium acetate (**14**) was obtained as a colorless waxy solid (Scheme 2). Alternatively, the same compound was also obtained by adding the acidic aluminum oxide to the reaction mixture containing the tertiary amine **13**, to afford its quaternization under otherwise identical conditions.

The two methylation approaches afforded either the tertiary amine **13** or the ammonium salt **14**, but did not offer access to the *N*-monomethylated, secondary amine, *N*-methyl-α-tocopheramine (**12**). To synthesize this compound, we used a previously developed approach for quantitative *N*-mono-demethylation of tertiary *N*-methylamines according to a facile chromatography-like setup [36]. The amine to be mono-demethylated passes slowly through a column with different reaction zones, the first one oxidizing the tertiary amine to the corresponding amine *N*-oxide, the second one effecting deoxygenative demethylation into secondary amine and HCHO, and the third one being the purification zone which removes the byproducts. The deoxygenative demethylation is based on the autocatalytic degradation of amine *N*-oxides by carbenium-iminium ions (Mannich intermediates) [14]. Based on this mechanism, demethylation occurs strictly just once in *N*,*N*-dimethylamino structures. This demethylation method, which has been reported to afford excellent yields for structurally diverse tertiary *N*-methylamines [36], worked also very well in the present case, giving a 94% yield of **12**. The solvent used in the original demethylation protocol, chloroform, was replaced by the more sustainable dihydrolevoglucosenone (cyrene®) [37] without yield penalty. Preliminary experiments indicated that also oxidation of the tertiary amine **13** by the laccase mediator system [38] caused *N*-demethylation to give *N*-methyl-α-tocopheramine (**12**) in good yields above 70%, but this approach was not further followed.

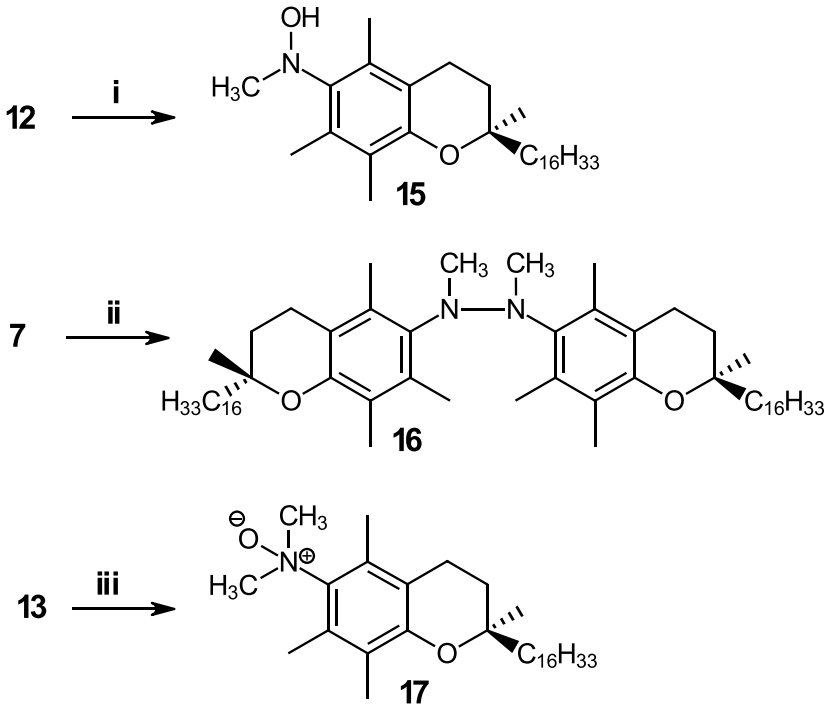
Table 1 summarizes the ^{1}H and ^{13}C NMR data of the *N*-methylated compounds **12**–**14** in comparison to parent amine **1**. The effects of *N*-methylation on the chemical shifts of the chroman system in α-tocopheramine are rather small, and no influence of methylation whatsoever on the chemical shifts of the isoprenoid side chain was seen. With increasing number of *N*-methyl groups, their ^{1}H NMR shift is down-field shifted from 2.44 to 2.52 and 3.84 ppm in **12**, **13**, and **14**, respectively. There was a peculiar down-field shift by 0.14 ppm for the H-3 methylene protons in the ammonium derivative **14**. *N*-Methylation caused a down-field shift of carbon resonances in the aromatic system, affecting in particular the *ortho*-carbon atoms C-5 and C-7 (9–14 ppm) and the *ipso*- and *para*-carbon atoms (4–6 ppm). These shift effects increased over the monomethylated compound **12** to the dimethylated derivative **13**, and are reduced again by quaternization (**14**). Quaternization causes a slight

Table 1 ^{1}H and ^{13}C chemical shifts (δ/ppm) of α-tocopheramine (**1**) and its *N*-methylated derivatives **12**–**14** in $CDCl_3$ as the solvent (25 °C)

Nucleus/position[a]	α-Tocopher-amine (**1**)	*N*-Methyl derivative **12**	*N*,*N*-Dimethyl derivative **13**	*N*,*N*,*N*-Trimethyl ammonium acetate deriv. **14**
H-2a	1.38 (s, 3H)	1.39 (s, 3H)	1.39 (s, 3H)	1.38 (s, 3H)
H-3	1.73 (m, 2H)	1.78 (m, 2H)	1.78 (m, 2H)	1.92 (m, 2H)
H-4	2.66 (“t”, 2H)	2.63 (“t”, 2H)	2.63 (“t”, 2H)	2.60 (“t”, 2H)
H-5a, 7a, 8b	2.16, 2.13, 2.09 (3×s, 3×3H)	2.18, 2.16, 2.11 (3×s, 3×3H)	2.18, 2.15, 2.11 (3×s, 3×3H)	2.24, 2.19, 2.14 (3×s, 3×3H)
N–H	4.9 (s, br, 1H)	1.49	–	–
N-Me	–	2.44/40.8	2.52/40.4	3.84/56.0
C-2	74.3 70.7	74.7	74.5	75.9
C-2a	28.0 27.2	27.8	27.7	28.1
C-3	32.7 32.8	32.7	32.9	31.3
C-4	22.7 23.5	22.3	22.6	21.0
C-5a, 7a, 8b	13.6, 12.6, 11.9	12.8, 12.6, 12.2	17.4, 13.0, 11.7	20.4, 20.0, 13.1
C-4a	122.3	123.2	123.4	126.4
C-5	117.1	126.5	131.1	129.3
C-6	134.7	138.6	140.1	135.9
C-7	117.8	126.6	130.1	128.0
C-8	120.6	119.6	121.2	123.9
C-8a	145.0	149.3	150.4	151.9

[a]Atom numbering see Scheme 1

Scheme 3



i = H_2O_2 (10 %, aq., 20 eq.), dioxane, reflux, 15 min, 84 %
ii = a) Me_2CO_3 (10 mL / 1 g of **7**), basic Al_2O_3 (Brockmann I, 5 wt. eq.), 120°C, 30 min, b) active C (0.5 wt. eq.), r.t., 5 min, 98 %
iii = H_2O_2 (30 %, aq., 5 eq.), dioxane, r.t., 30 min, 90 %

down-field shift also of the *meta*-carbon resonances, C-4a and C-8a (3 – 4 ppm), which was not seen in the case of **12** and **13**.

Stored in an inert gas atmosphere (Ar) in the dark, all three derivatives **12**–**14** were completely stable at room temperature. No discoloration was detectable even after storage over more than 6 weeks under these conditions. A comparison sample stored under air in the dark showed a slight yellow discoloration after 2 weeks which, however, did not become more pronounced upon longer storage. All three derivatives **12**–**14** are soluble in common organic solvents, are tolerant towards acids (1 M H_2SO_4, glacial acetic acid) and alkali (1 M NaOH). No instabilities or rearrangements, as for instance in the case of the nitroso-derivative **6** upon alkali treatment [18], were observed.

As mentioned introductorily, smaller amounts of the *N*-methyl derivative **12** and *N*,*N*-dimethyl derivative **13** have been tested preliminarily as stabilizers of cellulose spinning dopes in imidazolium ionic liquids against thermal and antioxidative degradation [13, 39]. By extraction of the aqueous spinning baths with petroleum ether, non-reacted tocopheramines and their reaction products were separated, being readily retrievable because of their strongly lipophilic nature due to the isoprenoid side chain. In addition to these tocopherol derivatives, the extract contained smaller amounts (11% of extracted mass) of benzoid/furanoid compounds, derived from thermal aging and oxidation of the polysaccharide components, cellulose and hemicelluloses [40], via furfural and 5-hydroxymethylfurfural intermediates [41]. In contrast to α-tocopheramine (**1**) with its rather extensive range of possible oxidation products (cf. Scheme 1), only two products were formed from *N*-methyl-α-tocopheramine (**12**): hydroxylamine **15** and *N*,*N*-dimethyl-*N*,*N*-bis(tocopheryl) hydrazine (**16**), and only one product from *N*,*N*-dimethyltocopheramine (**14**), namely *N*,*N*-dimethyl-α-tocopheramine *N*-oxide (**17**), see Scheme 3. Structural elucidation of these compounds was based on NMR (see Table 2) and MS data (experimental part) as well as the comparison with authentic, independently synthesized samples.

The tetrasubstituted hydrazine **16** was synthesized by methylation of the *N*,*N*-bis(tocopher)hydrazine **7**, which was available from previous work [18], see Scheme 3. The protocol was analogous to the ones used in Scheme 2. The amine *N*-oxide **17** was obtained by oxidation of the tertiary amine **13** with 30% hydrogen peroxide at room temperature in dioxane. Treatment of secondary amine **12** with 10%

Table 2 ^{1}H and ^{13}C chemical shifts (δ/ppm) of the *N*-methylated oxidation products **15**–**17** in comparison to the parent compound α-tocopheramine (**1**), measured in $CDCl_3$ (25 °C)

Nucleus/position[a]	α-Tocopheramine (**1**)	*N*-Methyl *N*–OH derivative **15**	*N*,*N*´-Dimethyl hydrazine derivative **16**	*N*,*N*-Dimethyl *N*-oxide derivative **17**
H-2a	1.38 (s, 3H)	1.40 (s, 3H)	1.37 (s, 3H)	1.33 (s, 3H)
H-3	1.73 (m, 2H)	1.77 (m, 2H)	1.77 (m, 2H)	1.59 (m, 2H)
H-4	2.66 ("t", 2H)	2.59 ("t", 2H)	2.65 ("t", 2H)	2.42 ("t", 2H)
H-5a, 7a, 8b	2.16, 2.13, 2.09 (3 × s, 3 × 3H)	2.17, 2.12, 2.11 (3 × s, 3 × 3H)	2.16, 2.14, 2.10 (3xs, 3 × 3H)	2.21, 2.18, 2.08 (3 × s, 3 × 3H)
N–H/N–OH	4.9 (s, br, 1H)	3.80 (s, br, 1H)	–	–
N-Me	–	3.08/46.2	2.28/39.4	3.36/52.9
C-2	74.3 70.7	75.0	74.6	74.2
C-2a	28.0 27.2	27.8	28.4	27.6
C-3	32.7 32.8	32.7	32.0	32.0
C-4	22.7 23.5	22.5	22.5	22.2
C-5a, 7a, 8b	13.6, 12.6, 11.9	16.4, 12.8, 12.0	12.6, 12.5, 12.2	16.4, 12.8, 11.4
C-4a	122.3	122.0	123.0	126.9
C-5	117.1	131.9	125.9	134.0
C-6	134.7	140.3	137.6	145.6
C-7	117.8	132.0	126.4	133.3
C-8	120.6	121.8	120.2	121.9
C-8a	145.0	151.2	148.5	149.4

[a]For atom numbering see Scheme 1

H_2O_2 under otherwise identical conditions, followed by treatment with aqueous sodium bisulfite solution, afforded hydroxylamine **15**. The reaction appeared to proceed via an intermediate, dark-red nitroxyl radical [22], which immediately gave the colorless hydroxylamine **15** upon reduction with bisulfite. Under inert conditions, however, the radical intermediate seemed to be persistent and unreactive towards common EMPO-type radical traps [42], maintaining its red color even after weeks.

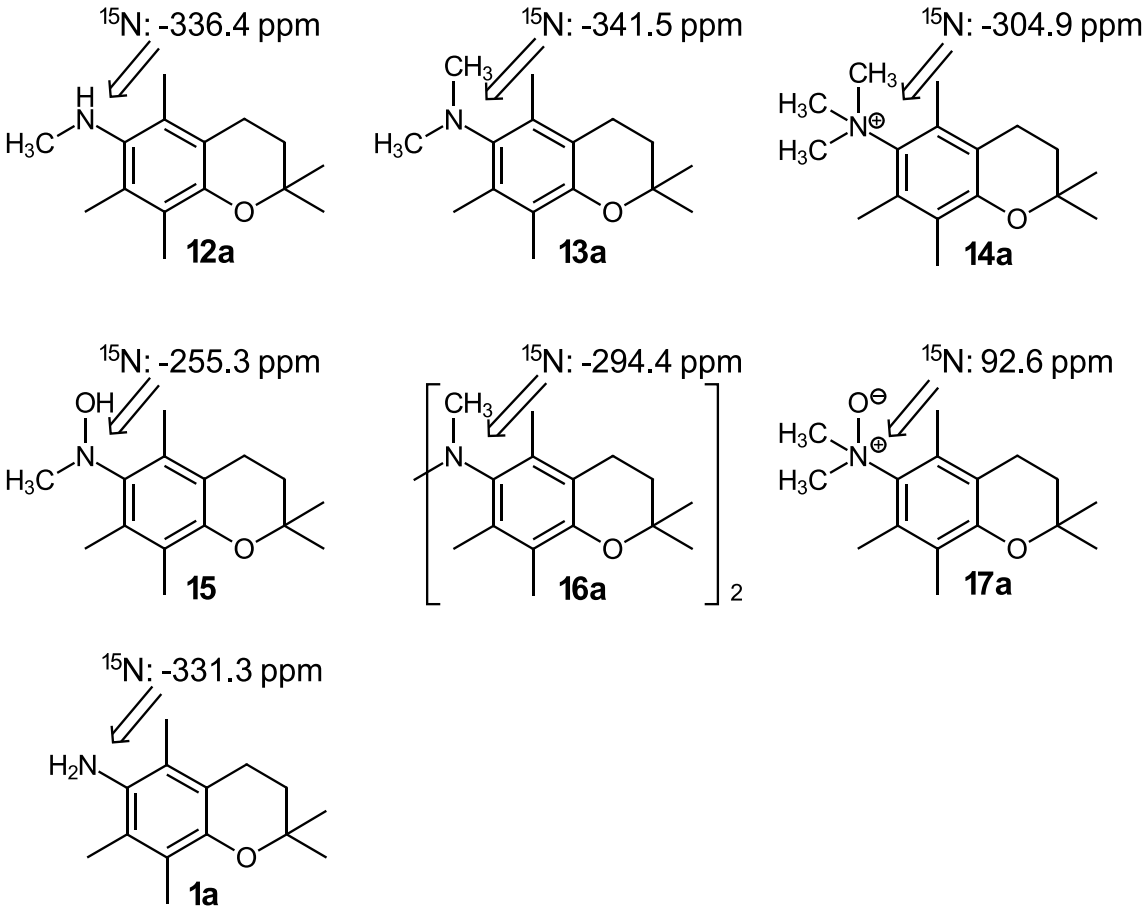
The ^{1}H and ^{13}C NMR data of the oxidation products **15**, **16**, and **17** are listed in Table 2, along with starting amine **1** for convenient comparison. The shift differences between *N*-methyl derivative **12** and its N–N-coupling product, hydrazine **16**, are very minor both in the ^{1}H (< 0.05 ppm) and ^{13}C domains (< 1 ppm); only the ^{1}H resonances of the *N*-methyl groups (2.44 in **12** vs. 2.28 in **16**) can be used for reliable distinction. In the *N*-hydroxy (**15**) and *N*-oxide (**17**) derivatives, the ^{13}C down-field shift effects on the *ortho*-, *ipso*- and *para*-carbon atoms were similar as discussed above (cf. Table 1). Note the down-field *N*-methyl shifts of 46.2 ppm in **15** and 52.9 ppm in **17** (relative to 40.8 ppm in *N*-methyl-α-tocopheramine **12**).

The tocopheramine derivatives **12**–**17** are distinguished only by different substituents and oxidation stages of the nitrogen. To differentiate them only based on their ^{1}H and ^{13}C NMR data can thus be rather challenging. ^{15}N NMR can provide a much better distinction [18, 19]: therefore, we used the ^{15}N-isotopically labeled model compound **1a**, in which the isoprenoid side chain is replaced by a methyl group, available from previous work [43], to synthesize the corresponding ^{15}N-isotopically labeled model compounds (**12a**-**17a**). By analogy, many earlier studies on compounds related to vitamin E (α-tocopherol) had relied on the corresponding truncated model compound 2,2,5,7,8-pentamethylchroman-6-ol [44, 45]. The ^{15}N chemical shifts of the *N*-methylated, isotopically labeled compounds (**12a**-**17a**) compounds fell in the expected ranges (Scheme 4), thus being in full support of the ^{1}H and ^{13}C NMR data. Given for comparison, the ^{15}N atom in **1a** resonates at -331.3 ppm (see Scheme 4). Note the large down-field shift (more positive value) of the nitrogen in the amine *N*-oxide **17a**.

Conclusion

Synthesis approaches towards *N*-methylated derivatives of α-tocopheramine (**12**–**14**) were developed, allowing the compounds to be prepared in facile one-pot procedures with yields of over 90% and in compliance with green chemistry principles. Any toxic reagents and solvents as well as the need for chromatographic purification are eliminated, and the procedures can be easily expanded to a scale of several 100 g and beyond. With these synthesis approaches at hand, sufficient amounts of the compounds can now be provided

Scheme 4



for comprehensive testing as stabilizers for cellulose solutions in ionic liquids in the area of fiber spinning. The performance of these compounds under different spinning conditions and their reactivity differences will be the topics of an upcoming account.

Experimental

All chemicals were commercial products, of the highest purity available and used without further purification. HPLC-grade solvents were used for all extractions and workup procedures. Bidistilled water was used for all aqueous extractions and for all aqueous solutions. Petroleum ether had a boiling range of 50—70 °C. 1,4-Dioxane, ethyl acetate, and toluene used in chromatography were distilled before use. α-Tocopheramine (**1**) was of the [*R*,*R*,*R*]-type, maintenance of stereochemical integrity over the reactions performed was not further checked, however.

All reactions involving non-aqueous conditions were conducted in oven-dried (140 °C, overnight) glassware under an argon atmosphere. TLC was performed using Merck silica get 60 F_{254} pre-coated plates, and flash chromatography on Baker silica gel (40 μm particle size). All products were purified to homogeneity by TLC / GC analysis; yields refer to isolated, pure products with satisfying elemental analysis data (±0.2). Elemental analyses were performed at the Microanalytical Laboratory of the University of Vienna. Melting points were determined on a Kofler-type micro hot stage with Reichert-Biovar microscope.

^{1}H NMR spectra were recorded at 300.13 MHz for ^{1}H and at 75.47 MHz for ^{13}C NMR in $CDCl_3$ if not otherwise stated. Chemical shifts, relative to TMS as internal standard, are given in δ values, coupling constants in Hz. ^{13}C peaks were assigned by means of APT, HMQC, and HMBC spectra.

The nomenclature and atom numbering of tocopherols and chromanols as recommended by IUPAC was used throughout [46, 47]. ^{1}H and ^{13}C NMR resonances of the isoprenoid side chain of tocopherols are only insignificantly influenced ($\Delta < 0.05$ ppm) by modifications of the chroman ring [48, 49], and are thus listed only once: 19.7 (C-4a′), 19.8 (C-8a′), 21.2 (C-2′), 22.7 (C-13′), 22.8

(C-12a′), 24.6 (C-6′), 24.8 (C-10′), 28.0 (C-12′), 32.6 (C-8′), 32.8 (C-4′), 37.3 (C-7′), 37.4 (C-9′), 37.5 (C-5′), 37.5 (C-3′), 39.3 (C-11′), 39.9 (C-1′) ppm. Analytical data for α-tocopheramine (**1**) agreed with the literature: [2] for methods apart from NMR, and [7] for NMR data, and so did the data for the ^{15}N-labeled model compound **1a** [43].

***N,N*-Dimethyl-[(*R*)-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-2,5,7,8-tetramethyl-6-chromanyl]-amine (6-desoxy-6-dimethylamino-α-tocopherol, *N,N*-dimethyl-*α*-tocopheramine, 13, $C_{31}H_{55}NO$)** In a stainless-steel autoclave with Teflon coating, 0.43 g α-tocopheramine (**1**, 1.00 mmol) was dissolved in 53.50 g freshly distilled dimethyl carbonate (50.00 cm^3). Basic aluminum oxide (2.15 g, Brockmann grade I) was added. The vessel was flushed with argon, sealed, heated to 120 °C (20°/min) and stirred for 30 min. Efficient agitation of the alumina was crucial to complete the reaction within the time used. After cooling to r.t., the vessel was opened, another aliquot of basic aluminum oxide (2.15 g, Brockmann grade I) was added, the mixture stirred for 5 min and filtered. The solid was washed with 20 cm^3 ice-cold dimethyl carbonate. The solvent of the combined organic phases was removed in vacuo at room temperature to provide 0.42 g (91%) of **13** as a colorless, viscous oil. R_f (toluene) = 0.50; ^{1}H NMR and ^{13}C NMR, see Table 1; EI-MS (70 eV): *m/z* = 459 (MH^+, 55), 458 (36), 232 (40), 191 (100), 57 (25), 44 (70), 43 (10); $[\alpha]_D^{20} = +4.4°$ cm^2 g^{-1} (*c* = 1, ethanol).

***N,N,N*-Trimethyl-[(*R*)-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-2,5,7,8-tetramethyl-6-chromanyl]ammonium acetate (*N,N,N*-trimethyl-*α*-tocopherammonium acetate, 14, $C_{34}H_{61}NO_3$)** In a stainless-steel autoclave with Teflon coating, 0.43 g α-tocopheramine (**1**, 1.00 mmol) was dissolved in 53.50 g freshly distilled dimethyl carbonate (50.00 cm^3). Acidic aluminum oxide (2.15 g, Brockmann grade I) was added. The vessel was flushed with argon, sealed, heated to 120 °C (20 °C/min) and stirred for 30 min. Efficient agitation of the alumina was crucial to complete the reaction within the time used. After cooling to r.t., the vessel was opened, 0.50 g active charcoal was added, the mixture stirred for 5 min and filtered through a 2 cm layer of celite. The solid was washed with 20 cm^3 ice-cold dimethyl carbonate. The solvent was evaporated in vacuo to a volume of about 10 cm^3, and 2 cm^3 glacial acetic acid was added, upon which the clear liquid turned cloudy due to evolved gases. After stirring for additional 30 min, vacuum (10^{-3} Torr) was applied for another 30 min. A waxy, colorless solid was obtained which was recrystallized from petroleum ether to afforded 0.48 g (91%) of **14** as colorless, waxy plates. R_f (toluene) = 0.18; ^{1}H NMR and ^{13}C NMR, see Table 1. EI-MS (70 eV): *m/z* = 473 ([M-Ac]$^+$, 85), 247 (50), 206 (100), 60 (30), 59 (40), 43 (15); $[\alpha]_D^{20} = -22.4°$ cm^2 g^{-1} (*c* = 1, ethanol).

***N*-Methyl-[(*R*)-2-[(4*R*,8*R*)-4,8,12-trimethyltridecyl]-2,5,7,8-tetramethyl-6-chromanyl]amine (6-desoxy-6-aminomethyl-*α*-tocopherol, *N*-methyl-*α*-tocopheramine, 12, $C_{30}H_{53}NO$)** The procedure used the previously published demethylation procedure [36], starting with 0.92 g N,*N*-dimethyl-α-tocopheramine (**13**, 2.00 mmol) and replacing chloroform by dihydrolevoglucosenone (cyrene®). After evaporation of the solvent, 0.83 g (94%) of **12** was obtained as colorless, viscous oil. R_f (toluene) = 0.42; ^{1}H NMR and ^{13}C NMR, see Table 1. EI-MS (70 eV): *m/z* = MS (70 eV): *m/z* = 445 (MH^+, 80), 444 (45), 218 (15), 177 (100), 57 (35), 43 (10); $[\alpha]_D^{20} = +62.4°$ cm^2 g^{-1} (*c* = 1, ethanol).

***N*-Methyl-(2,2,5,7,8-pentamethyl-6-chromanyl)amine (12a, $C_{15}H_{23}{}^{15}NO$)** The procedure follows the above protocol for the preparation of **12**, employing model compound **13a** (1 mmol, 0.25 g) instead of *N*,*N*-dimethyl-α-tocopheramine (**13**). Evaporation of the solvent in vacuo afforded a solid that was crystallized twice from *n*-heptane to afford 0.22 g (95%) of **12a**. M.p.: 80–81 °C; R_f (*n*-heptane / ethyl acetate, v/v = 10:1) = 0.44; ^{1}H NMR: δ = 2.63 (2H, t, ^3J = 7.2 Hz, 4-CH_2), 2.44 (3H, s, N-Me), 2.18 (s, 3H, 5a-CH_3), 2.16 (s, 3H, 7a-CH_3), 2.12 (s, 3H, 8b-CH_3) 1.80 (t, 2H, ^3J = 7.2 Hz, 3-CH_2), 1.35 (s, 6H, 2a-CH_3) ppm; ^{13}C NMR: δ = 149.2 (C-8a), 138.6 (C-6, d, C-6, $J_{C,N}$ = 24.0 Hz), 126.6 (C-7), 126.3 (C-5), 122.9 (C-4a), 120.0 (C-8), 74.0 (C-2), 40.2 (N-Me), 32.4 (C-3), 27.5 (C-2a), 22.4 (C-4), 12.9 (C-7a), 12.7 (C-5a), 12.0 (C-8b) ppm; ^{15}N NMR: δ = – 336.4 ppm.

***N,N*-Dimethyl-(2,2,5,7,8-pentamethyl-6-chromanyl)amine (13a, $C_{16}H_{25}{}^{15}NO$)** The procedure follows the above protocol for the preparation of **13**, applying model compound **1a** (1 mmol) instead of α-tocopheramine (**1**). Evaporation of the solvent in vacuo and flash chromatography (*n*-heptane / ethyl acetate, v/v = 10:1) afforded 0.24 g (96%) of **13a**. M.p.: 42–44 °C; R_f (*n*-heptane / ethyl acetate, v/v = 10:1) = 0.69; ^{1}H NMR: δ = 2.63 (2H, t, ^3J = 7.0 Hz, 4-CH_2), 2.50 (6H, s, N-Me), 2.17 (s, 3H, 5a-CH_3), 2.16 (s, 3H, 7a-CH_3), 2.12 (s, 3H, 8b-CH_3), 1.79 (t, 2H, ^3J = 7.0 Hz, 3-CH_2), 1.36 (s, 6H, 2a-CH_3) ppm; ^{13}C NMR: δ = 150.0 (C-8a), 141.1 (d, C-6, $J_{C,N}$ = 18.6 Hz), 130.9 (C-5), 129.8 (C-7), 123.4 (C-4a), 121.4 (C-8), 74.5 (C-2), 40.9 (N-Me), 33.2 (C-3), 27.0 (C-2a), 21.2 (C-4), 17.2 (C-7a), 13.8 (C-5a), 11.8 (C-8b) ppm; ^{15}N NMR: δ = – 341.5 ppm.

***N,N,N*-Trimethyl-(2,2,5,7,8-pentamethyl-6-chromanyl)-ammonium acetate (14a, $C_{19}H_{31}{}^{15}NO_3$)** The procedure follows the above protocol for the preparation of **14**, employing model compound **1a** (1 mmol) instead of α-tocopheramine (**1**). Evaporation of the solvent in vacuo and flash chromatography (*n*-heptane / ethyl acetate, v/v = 10:1) afforded 0.26 g (82%) of **14a**. M.p.: 133–136 °C (decomp.); R_f (*n*-heptane / ethyl acetate, v/v = 10:1) = 0.12; ^{1}H NMR: δ = 3.86 (s,

9H, N-Me), 2.58 (2H, t, $^{3}J = 6.4$ Hz, 4-CH_2), 2.22 (s, 3H, 5a-CH_3), 2.18 (s, 3H, 7a-CH_3), 2.12 (s, 3H, 8b-CH_3) 1.93 (t, 2H, $^{3}J = 6.8$ Hz, 3-CH_2), 1.36 (s, 6H, 2a-CH_3) ppm; ^{13}C NMR: $\delta = 150.4$ (C-8a), 136.1 (d, C-6, $J_{C,N} = 26.6$ Hz), 129.3 (C-5), 128.4 (C-7), 126.4 (C-4a), 123.0 (C-8), 74.5 (C-2), 52.2 (N-Me), 30.5 (C-3), 29.0 (C-2a), 20.2 (C-4), 19.2 (C-7a), 18.8 (C-5a), 13.8 (C-8b) ppm; ^{15}N NMR: $\delta = -304.9$ ppm.

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