



New Synthesis of ($\pm$)- α -CMBHC and Its Confirmation as a Metabolite of α -Tocopherol (Vitamin E)

Simon A.S. Pope,^a Guillaume E. Burtin,^b Peter T. Clayton,^a David J. Madge^{b,*}
and David P.R. Muller^a

^aBiochemistry, Endocrinology and Metabolism Unit, The Institute of Child Health, University College London,
London, WC1N 1EH, UK

^bBiological and Medicinal Chemistry, The Wolfson Institute for Biomedical Research, University College London,
London, WC1E 6AU, UK

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Abstract—There is currently interest in the metabolism of the various compounds which make up the vitamin E family, especially with regards to the possible use of vitamin E metabolites as markers of oxidative stress and adequate vitamin E supply. A number of vitamin E metabolites have been described to date and we have recently developed a method to extract and quantitate a range of vitamin E metabolites in human urine. During the development of this method a new metabolite of α -tocopherol was identified, which we tentatively characterised as 5-(6-hydroxy-2,5,7,8-tetramethyl-chroman-2-yl)-2-methyl-pentanoic acid (α -CMBHC).¹ Here we describe the synthesis of α -CMBHC as a standard and confirm that it is a metabolite of α -tocopherol. © 2001 Elsevier Science Ltd. All rights reserved.

Introduction

α -Tocopherol (**1**) is the major lipid soluble antioxidant in vivo and is a member of the vitamin E family.^{2,3} Vitamin E is a generic term describing the tocopherols and tocotrienols, which have saturated and unsaturated side-chains respectively (Fig. 1). Each group has α , β , δ and γ forms which differ in the number and position of methyl groups on the chroman ring. α -Tocopherol (**1**) is the most abundant form in the body accounting for over 90% of the total vitamin E retained, even though γ -tocopherol is generally the most abundant form in the diet.^{4,5} Naturally occurring α -tocopherol is a single stereoisomer designated *R,R,R*- α -tocopherol whereas most synthetic supplements are a mixture of the eight possible stereoisomers arising from the three chiral centres.

Over the last 50 years a number of vitamin E metabolites have been described and recently there has been renewed interest in measuring urinary metabolites of vitamin E due to their proposed use as biomarkers of oxidative stress and adequate vitamin E supply.⁶ Scheme 1 shows an overview of the proposed metabolism of α -tocopherol. In the 1950's α -tocopheronic acid

(**2**) and its lactone, α -tocopheronolactone (**3**), the so-called Simon metabolites, were characterised in the urine of animals and man.^{7,8} These metabolites, which result from the ring opening of the chroman moiety, were thought to be products of α -tocopherol oxidation. More recently another α -tocopherol metabolite, 3-(6-hydroxy-2,5,7,8-tetramethyl-chroman-2-yl)-propionic acid (α -CEHC)¹ (**4**), has been described and found to be the major urinary metabolite of α -tocopherol.⁶ α -CEHC (**4**) has an intact chroman ring and was hypothesised to represent excretion of excess α -tocopherol. Analogous CEHC metabolites have also been described for δ - and γ -tocopherol.^{9,10} Along with the identification of α -CEHC (**4**) as the major metabolite of α -tocopherol came the hypothesis that the previously identified Simon metabolites were produced by artefactual oxidation of α -CEHC during the extraction procedure.⁶ Recently we have reported a longer side-chain metabolite of α -tocopherol that was tentatively identified as 5-(6-hydroxy-2,5,7,8-tetramethyl-chroman-2-yl)-2-methyl-pentanoic acid (α -CMBHC) (**5**) (Scheme 1).¹¹ The equivalent metabolite of γ -tocopherol has also been described by Parker et al.¹² The metabolites of the various tocopherols would be expected to retain the stereochemistry of the parent compound from which they are derived. For example, metabolites produced from synthetic vitamin E would be present as a mixture of isomers while those

*Corresponding author. Tel.: +44-020-76796712; fax: +44-020-76796799;
e-mail: d.madge@ucl.ac.uk

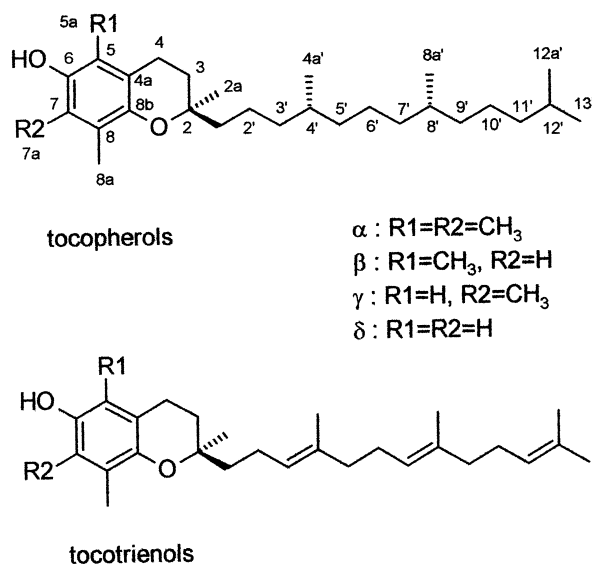


Figure 1. The structures of the naturally occurring forms of vitamin E.

produced from naturally occurring vitamin E would be present as single isomers. Indeed, the stereochemistry of γ -CEHC, derived from *R,R,R*- γ -tocopherol, has been shown to be *S*(+), meaning it is formed without epimerisation at C-2.¹³

In order to unambiguously confirm the structure of this new metabolite of α -tocopherol, we prepared a synthetic standard of α -CMBHC (**5**) and showed that it had GC–MS characteristics identical to those of the urinary metabolite.

Results

In studies to elucidate the metabolism of α -tocopherol we developed a new extraction procedure and GC–MS method for human urinary vitamin E metabolites.¹¹ This method, which requires trimethylsilyl-derivatisation of deconjugated metabolites, allowed us to analyse a range of metabolites, including α -tocopheronolactone (**6**) and α -CEHC (**4**). During these studies we observed a minor, late eluting peak in human urine which had a mass spectra displaying a major fragment ion (*m/z* 237) in common with silylated α -CEHC (**4**), but with a molecular ion of *m/z* 464, which is 42 daltons greater than the molecular ion of silylated α -CEHC (Fig. 2). After ingestion of *d*₆- α -tocopherol,¹⁴ this unknown peak increased in size and the mass spectrum showed an increase in mass of 6 daltons for both the molecular ion and the major fragment ion, confirming the unknown peak as a metabolite of α -tocopherol. This unknown peak was tentatively identified as α -CMBHC (**5**) based on the GC–MS data and on the expected side-chain metabolism of α -tocopherol. Although on biological grounds α -CMBHC (**5**) was the most likely structure due to the hypothesised β -oxidation of the phytyl side-chain, other structures could display similar chromatography and mass spectra. The structure of the unknown metabolite has now been confirmed by the unambiguous synthesis of α -CMBHC (**5**).

A synthesis of ($\pm$)- α -CMBHC (**5**) was described by Weichert et al. more than 30 years ago.¹⁵ However, this report did not propose α -CMBHC (**5**) as a metabolite of α -tocopherol and did not include NMR characterisation. The strategy relied upon the condensation of 6-hydroxy-6-vinyl-2-methylheptanoic acid (**7**) with 2,3,5-trimethylhydroquinone (**8**) (TMHQ) in the presence of a mixture of zinc chloride and boron trifluoride–diethyl etherate complex. The allylic alcohol (**7**) was obtained in three steps by oxidative ring opening of dimethylcyclohexanone (**9**), addition of acetylide to the resulting 6-oxo-2-methylheptanoic acid (**10**) and final catalytic hydrogenation of the propargylic alcohol intermediate.¹⁶

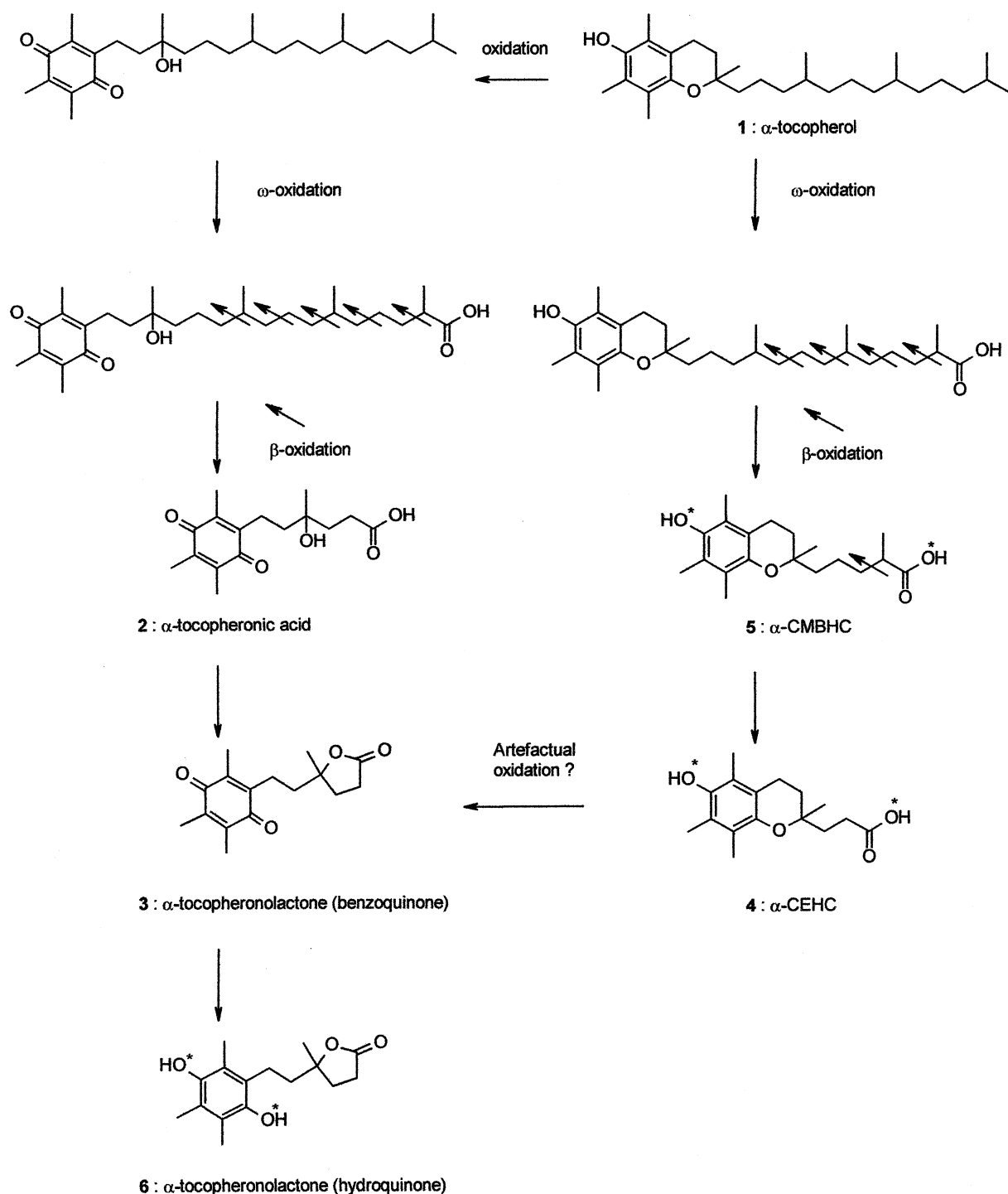
In our synthesis of ($\pm$)- α -CMBHC (**5**), the ketoacid (**10**) was prepared in a good yield by treatment of dimethylcyclohexanone (**9**) with potassium permanganate according to the procedure described by Weichert et al.¹⁵ However, we decided to synthesise the key intermediate (**7**) by condensation of vinyl magnesium bromide with 6-oxo-2-methylheptanoic acid (**10**) (Scheme 2). Preliminary studies on a commercially available model compound (6-oxo-heptanoic acid) suggested that the Grignard condensation would be more effective on the corresponding methyl ester (**11**). 6-Hydroxy-6-vinyl-2-methylheptanoic acid methyl ester (**12**) was thus prepared by condensation of vinyl magnesium bromide with 6-oxo-2-methylheptanoic acid methyl ester (**11**), which was obtained from the corresponding acid (**10**). A similar strategy was used by Wechter and Kantoci to prepare the key intermediate, γ -methyl- γ -vinyl-butyrolactone, for their syntheses of α - and γ -CEHC.^{10,13}

Condensation of 6-hydroxy-6-vinyl-2-methylheptanoic acid methyl ester (**12**) with TMHQ (**8**) was performed according to the conditions described by Kantoci et al.¹³ The allylic alcohol (**12**) was added at 110 °C over 3 h to a solution of TMHQ (**8**) and boron trifluoride–diethyl etherate complex in dioxane to give α -CMBHC methyl ester (**13**) in 80% yield. Saponification of the methyl ester (**13**) using aqueous sodium hydroxide afforded ($\pm$)- α -CMBHC (**5**).

Using the synthetic standard ($\pm$)-(**5**) in our GC–MS analytical method, we confirmed that the retention times and mass spectra for the unknown metabolite and synthetic α -CMBHC (**5**) were identical. This was achieved by running the standard and urine extract separately and then in combination to show co-elution of the two peaks (Fig. 3). We assumed that the other peaks observed in urine samples with similar mass spectra, but with molecular and fragment ions 14 or 28 daltons less, correspond to γ - and δ -CMBHC respectively. The mass spectrum observed for the presumed γ -CMBHC agrees with that reported by Parker et al.¹²

Discussion

Vitamin E, and in particular α -tocopherol (**1**), is the major fat soluble antioxidant *in vivo*, protecting cellular membranes and other lipids against oxidative damage caused by oxygen-derived free radicals.^{2,3} Owing to the



Scheme 1. An overview of the proposed metabolism of α -tocopherol. The metabolites are thought to be excreted in the urine as sulphate or glucuronide conjugates. Possible sites of conjugation are indicated (*).

lipophilicity of vitamin E, lipoproteins and transfer proteins are required to deliver vitamin E around the body and transfer it between membranes.¹⁷ At high concentrations the various forms of vitamin E are likely to overload these transport/transfer mechanisms, leading to side-chain shortening of excess vitamin E and excretion of the resulting metabolites, such as α -CEHC (4), in the form of water soluble conjugates.⁶ In the present work, we confirmed that α -CMBHC (5) is a metabolite of α -tocopherol using a synthetic standard.

Other peaks observed using our GC–MS method have mass spectra consistent with the structures of δ - and γ -CMBHC, supporting the idea of a common pathway for the side-chain metabolism of all the tocopherols. The structure of the CMBHCs agrees with the postulated ω - and then β -oxidation of the phytyl side-chain, which is believed to occur in the peroxisome.¹⁸

Since the CMBHCs are the probable precursors of the CEHCs, metabolites with longer side-chains, corresponding

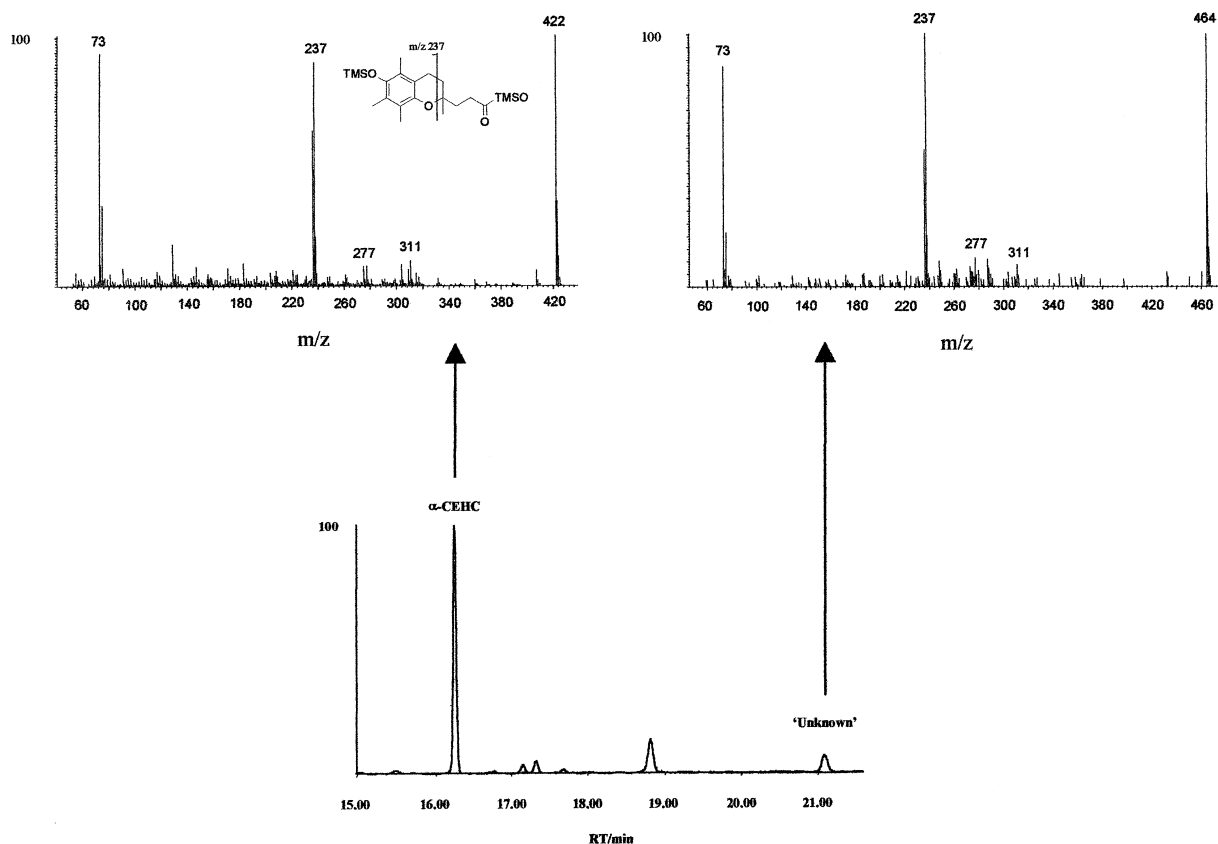
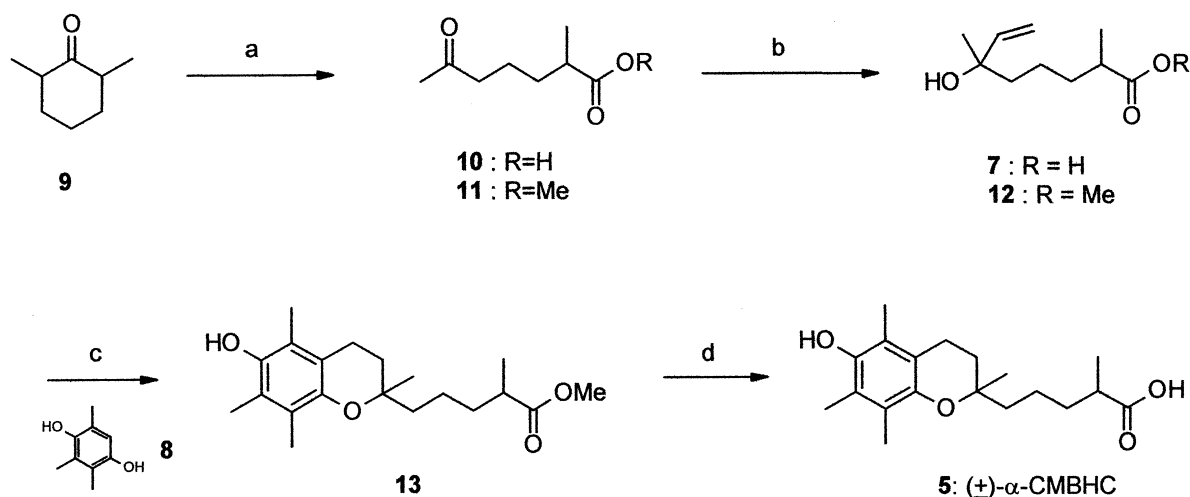


Figure 2. Gas chromatogram showing elution of the silyl derivatives of α -CEHC and the 'unknown' metabolite with their corresponding mass spectra.



Scheme 2. Synthesis of (±)- α -CMBHC (**5**). (a) (i) KMnO_4 ; (ii) MeOH , H^+ ; (b) CH_2CHMgBr ; (c) $\text{BF}_3 \cdot \text{Et}_2\text{O}$; (d) $\text{NaOH}/\text{H}_2\text{O}$.

to the precursors of the CMBHCs, are also possible. However, longer side-chain metabolites may not be excreted in the urine due to their greater hydrophobicity. It is also possible that longer side-chain metabolites would only be excreted when the metabolic pathways leading to complete side-chain oxidation are overloaded, such as after supplementation with a large amount of vitamin E.

The synthetic pathway we have developed for the preparation of (±)- α -CMBHC, could also be used to synthesise the CMBHC metabolite standards of the other tocopherols from the appropriately methylated hydroquinones. Although the CMBHCs are metabolic products of vitamin E we cannot rule out the possibility that they may have biological activity themselves. Recently γ -CEHC, a metabolite of γ -tocopherol, has

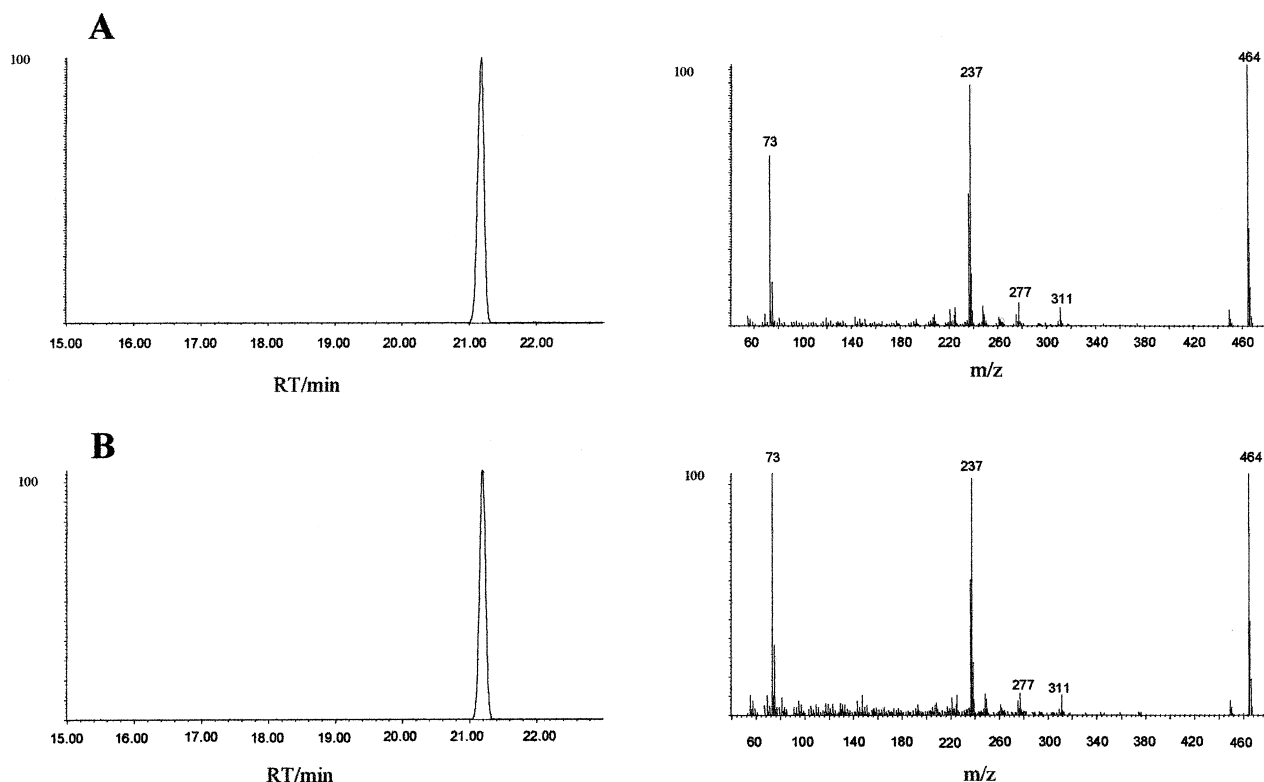


Figure 3. A shows an extracted ion chromatogram (m/z 464) of the silyl derivative of α -CMBHC standard (**5**) with its corresponding mass spectrum. B shows the equivalent data for a mixture of α -CMBHC standard and the 'unknown' urinary metabolite, showing co-elution of the two peaks and identical mass spectra.

been shown to act as a natriuretic factor by inhibiting potassium channels in kidney.¹⁰ The synthetic CMBHC standards could be used in initial investigations of their biological activity. However, it is worth noting that in the case of in vivo studies or enzymatic assays which require standards of the naturally occurring pure metabolite, synthetic methods allowing tighter control of the chiral centres will have to be used.

Conclusion

We have developed an efficient strategy for the synthesis ($\pm$)- α -CMBHC (**5**) and have used our synthetic material as a standard to confirm that α -CMBHC (**5**) is a minor metabolite of α -tocopherol (**1**) in human urine. ($\pm$)- α -CMBHC (**5**) has been synthesised in five steps and 19% overall yield from dimethylcyclohexanone (**9**) and has been fully characterised. This methodology could also be used to synthesise standards of δ - and γ -CMBHC, which both appear to be present in human urine.

Experimental

Extraction and analysis of urinary metabolites of vitamin E

The method used for the extraction and analysis of the vitamin E metabolites in this study was the same as that previously described.¹¹ In summary, the metabolites

were extracted from human urine, after acidification and addition of Trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid) and d_0 - α -CEHC standards,¹⁴ using C4 solid phase extraction (SPE) cartridges. Enzymatic deconjugation overnight with mixed β -glucuronidase/sulphatase and re-extraction using a second C4 SPE cartridge gave unconjugated metabolites. Trimethylsilyl (TMS) derivatives were produced using *N,O*-bis-(trimethylsilyl)trifluoroacetamide (BSTFA, Pierce and Warriner Ltd) at 60 °C for 1 h. The derivatised mixture (2 μ L) was injected (using a splitless technique) onto a DB1 fused silica column (30 m, 0.25 mm ID, 0.25 μ m film thickness; Jones Chromatography Ltd) in a Hewlett-Packard 5890 Series II gas chromatograph linked to a Hewlett-Packard 5970 mass-selective detector and Chem Station data system. The oven was maintained at 120 °C for 2 min, then ramped to 200 °C at 20 °C/min, to 240 °C at 2 °C/min, to 300 °C at 50 °C/min and finally held at 300 °C for 5 min. The ionisation energy was 70 eV. d_6 - α -Tocopherol metabolites were produced in the urine following supplementation with 300 mg d_6 - α -tocopherol,¹⁴ as previously described.¹¹ The metabolites and standard peaks were visualised by extracting the following ion chromatograms: Standards—Trolox, m/z 394, 237; d_0 - α -CEHC, m/z 431, 246; Metabolites- d_0 - α -CEHC/tocopheronolactone, m/z 422, 237; d_6 - α -CEHC/tocopheronolactone, m/z 428, 243; d_0 - γ -CEHC, m/z 408, 223; d_0 - α -CMBHC, m/z 464, 237; d_6 - α -CMBHC, m/z 470, 243; d_0 - γ -CMBHC, m/z 450, 223; d_0 - δ -CMBHC, m/z 436, 209.

Synthesis of (±)-5-(6-hydroxy-2,5,7,8-tetramethyl-chroman-2-yl)-2-methyl-pentanoic acid ((±)- α -CMBHC) (5)

General. All starting materials were either commercially available or reported previously in the literature unless noted. Solvents and reagents were used without further purification except tetrahydrofuran (THF) which was dried over sodium. Reactions were monitored by TLC on precoated silica gel plates (Kieselgel 60 F₂₅₄, Merck). Purification was performed by flash chromatography using silica gel (particle size 40–63 μ m, Merck). ¹H and ¹³C NMR spectra were recorded on a Bruker AMX-300 spectrometer. Chemical shifts are reported as ppm relative to tetramethylsilane (TMS) as internal standard. The chemical shifts of compounds (13) and (5) were assigned on the basis of ¹H–¹³C NMR correlation and previously published data.¹⁰ Atom numbering follows IUPAC convention. Mass spectra were recorded on either a VG ZAB SE spectrometer (electron impact and fast atom bombardment (FAB)) or a Micromass Quattro electrospray LC-mass spectrometer. IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrophotometer. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected.

6-Oxo-2-methyl-heptanoic acid (10). 2,6-Dimethyl-cyclohexanone (9) (1 g, 7.9 mmol) was added at room temperature to a stirring solution of potassium permanganate (1.76 g, 11.0 mmol) in water (60 mL). The reaction mixture was stirred at room temperature for 12 h, acidified with 5% aqueous hydrochloric acid and extracted in ethyl acetate. The organic layer was washed with water, dried over anhydrous magnesium sulphate and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (10–40% ethyl acetate in cyclohexane) to give (10) as a clear oil (1.0 g, 80%). IR (neat) 3700–2700 (acid), 1704 (carbonyl) cm^{-1} ; ¹H NMR (CDCl₃) δ 1.2 (3H, d, $J=7.2$ Hz, CHMe), 1.40–1.49 (1H, m, CHMe), 1.57–1.68 (3H, m), 2.14 (3H, s, COMe), 2.43–2.51 (3H, m); ¹³C NMR (CDCl₃) δ 17.1, 21.6, 30.2, 33.1, 39.5, 43.7, 183.0, 209.3; MS (FAB+) m/z 113 [M–CO₂H]⁺, 141 [M–OH]⁺, 159 [M+H]⁺.

6-Oxo-2-methyl-heptanoic acid methyl ester (11). A few drops of concentrated sulphuric acid were added at room temperature to a stirring solution of 6-oxo-2-methyl-heptanoic acid (10) (1.0 g, 6.3 mmol) in dry methanol (30 mL) under nitrogen. The reaction mixture was refluxed for 2 h and then an excess of ethyl acetate was added. The organic layer was washed successively with saturated aqueous sodium bicarbonate and water, dried over anhydrous magnesium sulphate and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (10–30% ethyl acetate in cyclohexane) to give (11) as an oil (820 mg, 76%). IR (neat) 1727 (carbonyl) cm^{-1} ; ¹H NMR (CDCl₃) δ 1.11 (3H, d, $J=6.8$ Hz, CHMe), 1.35–1.45 (1H, m), 1.47–1.70 (3H, m), 2.09 (3H, s, Me), 2.35–2.45 (3H, m), 3.63 (3H, s, OMe); ¹³C NMR (CDCl₃) δ 14.1, 17.0, 21.4, 29.7, 33.1, 39.2, 43.3, 51.4, 176.7, 208.2; MS (FAB+) m/z 113 [M–CO₂Me]⁺, 141 [M–OMe]⁺, 173 [M+H]⁺.

6-Hydroxy-6-vinyl-2-methyl-heptanoic acid methyl ester (12). Vinyl magnesium bromide (1M in THF, 6.4 mL, 6.4 mmol) was added dropwise at 0 °C to a stirring solution of 6-oxo-2-methyl-heptanoic acid methyl ester (11) (1 g, 5.8 mmol) in THF (5 mL) under nitrogen. The reaction was stirred at 0 °C for 2 h and then a few drops of water were added. The mixture was dried over anhydrous magnesium sulphate and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (10–30% ethyl acetate in cyclohexane) to give (12) as an oil and a mixture of two diastereoisomers (945 mg, 81%). IR (neat) 3416 (hydroxy), 1727 (carbonyl) cm^{-1} ; ¹H NMR (CDCl₃) δ 1.13 (3H, d, $J=7.2$ Hz, CHMe), 1.27 (3H, s, Me), 1.25–1.70 (6H, m, 3 $\times$ CH₂), 2.37–2.49 (1H, m, CHMe), 3.65 (3H, s, OMe), 5.02 (1H, dd, $J=10.6$, 1.1 Hz, CH₂=), 5.18 (1H, dd, $J=17.3$, 1.1 Hz, CH=), 5.88 (1H, dd, $J=17.3$, 10.6 Hz, CH₂=); ¹³C NMR (CDCl₃) δ 17.3, 21.8, 27.8, 34.3, 39.6, 42.3, 51.7, 73.2, 111.8, 145.3, 177.5; second diastereoisomer 17.4, 28.0, 42.4; MS (FAB+) m/z 183 [M–OH]⁺, 201 [M+H]⁺.

(±)-5-(6-Hydroxy-2,5,7,8-tetramethyl-chroman-2-yl)-2-methyl-pentanoic acid methyl ester (13). 6-Hydroxy-6-vinyl-2-methyl-heptanoic acid methyl ester (12) (830 mg, 4.15 mmol) in dioxane (1 mL) was added over 3 h at 110 °C to a stirring solution of 2,3,5-trimethylhydroquinone (421 mg, 2.77 mmol) and boron trifluoride diethyletherate (680 μ L, 5.5 mmol) in dioxane (15 mL) under nitrogen. The reaction mixture was cooled to room temperature and diluted with an excess of ethyl acetate. The organic layer was washed with water, dried over anhydrous magnesium sulphate and concentrated under vacuum. The crude compound was purified by flash chromatography on silica (10–30% ethyl acetate in cyclohexane) to give (13) as an oil and a mixture of two diastereoisomers (740 mg, 80%). IR (neat) 3439 (hydroxy), 1727 (carbonyl) cm^{-1} ; ¹H NMR (CDCl₃) δ 1.16 (3H, d, $J=6.9$ Hz, H4a'), 1.22 (3H, s, H2a), 1.41–1.71 (6H, m, 3 $\times$ CH₂), 1.78 (2H, ddd, $J=6.4$, 12.5, 13.4 Hz, CH₂), 2.11 (3H, s, H5a), 2.12 (3H, s, H7a), 2.17 (3H, s, H8a), 2.41–2.50 (1H, m, H4'), 2.60 (2H, t, $J=6.8$ Hz, H4) 3.67 (3H, s, OMe); ¹³C NMR (CDCl₃) δ 11.6 (C5a), 12.1 (C7a), 12.6 (C8a), 17.3 (C4a'), 21.0 (C4), 21.5 (CH₂), 23.9 (C2a), 31.8 (CH₂), 34.5 (CH₂), 39.5 (CH₂), 39.6 (C4'), 51.8 (OMe), 74.6 (C2), 117.5 (C5), 119.0 (C4a), 121.6 (C7), 122.8 (C8), 145.0 (C6), 145.6 (C8b), 177.6 (C5'); second diastereoisomer 17.4 (C4a'), 21.6 (CH₂), 39.6 (CH₂), 39.7 (C4'), 51.9 (OMe), 177.7 (C5'); MS (EI) m/z 165 (100%), 334 (72%, [M]⁺).

(±) 5-(6-Hydroxy-2,5,7,8-tetramethyl-chroman-2-yl)-2-methyl-pentanoic acid (5). Sodium hydroxide (50 mg, 1.25 mmol) in water (10 mL) was added at rt to a stirring solution (±)-5-(6-hydroxy-2,5,7,8-tetramethyl-chroman-2-yl)-2-methyl-pentanoate (13) (130 mg, 0.39 mmol) in methanol (10 mL). The reaction mixture was refluxed for 2 h, acidified to pH 3 with 5% aqueous hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous magnesium sulphate and concentrated under vacuum. The crude product was purified by flash chromatography on silica (20–30% ethyl acetate in cyclohexane) to yield (5)

as a solid and mixture of two diastereoisomers (60 mg, 48%). Mp 90–92 °C [reported 100–103 °C];¹⁴ IR (CHCl₃) 3700–2600 (acid + hydroxy), 1697 (carbonyl) cm⁻¹; ¹H NMR (CDCl₃) δ 1.16 (3H, d, *J* = 6.4 Hz, H4a'), 1.23 (3H, s, H2a), 1.41–1.61 (6H, m, 3×CH₂), 1.79 (2H, ddd, *J* = 6.6, 12.1, 13.4 Hz, CH₂), 2.12 (6H, s, H5a and H7a), 2.16 (3H, s, H8a), 2.46–2.55 (1H, m, H4'), 2.61 (2H, t, *J* = 6.4 Hz, H4); ¹³C NMR (CDCl₃) δ 11.6 (C5a), 12.1 (C7a), 12.6 (C8a), 17.2 (C4'a), 21.0 (C3'), 21.6 (CH₂), 24.0 (C2a), 31.9 (CH₂), 34.2 (CH₂), 39.7 (C4'), 39.8 (CH₂), 74.6 (C2), 117.6 (C5), 119.0 (C4a), 121.5 (C7), 122.9 (C8), 144.9 (C6), 145.7 (C8b), 183.5 (CO₂H); second diastereoisomer 17.3 (C4'a), 21.7 (CH₂), 39.7 (CH₂), 39.8 (C4'); MS (EI) *m/z* 165 (100%), 320 (22%, [M]⁺); FAB HRMS: calculated (M–H): 319.1908, found 319.1881 (C₁₉H₂₈O₄).

Acknowledgements

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References and Notes

- The names used for the metabolites of vitamin E discussed in this report conform with IUPAC nomenclature. However, several of the compounds mentioned herein are also commonly known by less systematic names. These are as follows: α-CEHC, 2,5,7,8-tetramethyl-2-(2-carboxy-2-ethyl)-6-hydroxy-chroman; α-CMBHC, 2,5,7,8-tetramethyl-2-(4-carboxy-2-methyl-butyl)-6-hydroxychroman. The correct IUPAC names for the other vitamin E metabolites mentioned in the text are: α-tocopheronolactone, 2,3,5-Trimethyl-6-[2-(2-methyl-5-oxo-tetrahydrofuran-2-yl)-ethyl]-[1,4]benzoquinone; γ-CEHC, 3-(6-Hydroxy-2,7,8-trimethyl-chroman-2-yl)-propionic acid; γ-CMBHC, 5-(6-Hydroxy-2,7,8-trimethyl-chroman-2-yl)-2-methyl-pentanoic acid; δ-CEHC, 3-(6-Hydroxy-2,8-dimethyl-chroman-2-yl)-propionic acid; δ-CMBHC, 5-(6-Hydroxy-2,8-dimethyl-chroman-2-yl)-2-methyl-pentanoic acid.
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