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Easy route to labeled and unlabeled *R*,*R*,*R*-γ-tocopherol by aryl demethylation of α-homologues

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Abstract—The interest in vitamin E research is increasingly focusing on the peculiar properties of the less investigated tocopherols and their metabolites, such as γ-tocopherol, which have been revealed as very important for human health. Metabolic studies of γ-tocopherol have been constricted by its high cost and the poor availability of stable isotope-labeled forms. An efficient, inexpensive and simple route is described for the preparation of labeled and unlabeled *R*,*R*,*R*-γ-tocopherol, starting from *R*,*R*,*R*-α-tocopherol, through simple thermal decarboxylation of γ-tocopherol-5-carboxylic acid.

1. Introduction

Vitamin E is the most important fat-soluble chain-breaking antioxidant. The term vitamin E covers all tocols and tocotrienols derivatives exhibiting qualitatively the biological activity of α-tocopherol.[1] The most important members of vitamin E family for human nutrition are represented by α- and γ-tocopherol, the former having much higher vitaminic activity and bioavailability,[2–4] and thus constituting the primary and almost exclusive form in supplements. Despite, the much lower plasma concentration and bioactivity compared to α-tocopherol, as assessed in animal bioassays, recent and growing evidence suggests that γ-tocopherol has unique properties that may be very important to human health, not shared by α-tocopherol.[5] Those features do not appear to be related to its chemical antioxidant behavior, but rather reflect anti-inflammatory, antineoplastic, and natriuretic functions possibly mediated through specific binding interactions. Moreover, epidemiological data suggest that γ-tocopherol is a better negative risk factor for certain types of cancer and myocardial infarction than is α-tocopherol.[6] All these findings have given a great boost to the research in the field of vitamin E, which is currently represented more and more by in vivo studies on tocopherols metabolites and γ-tocopherol. The utilization of stable isotope-labeled analogues greatly facilitates carrying out such studies.[7] In fact, they represent a powerful tool in terms of both specificity and sensitivity, acting as probes in the body and as internal standards for accurate quantitative determinations by specific techniques like mass spectrometry,[8–10] more and more used for the characterization of such complex matrices.

Isotope-labeled forms of γ-tocopherol are not readily available, and very few papers have been reported regarding their synthesis. Woggon et al. described a preparation of [7-methyl-^{3}H,^{14}C]-γ-tocopherol that is rather long and complicated,[11] and an enzymatic route to monodeuterated γ-tocopherol on very small scale (5 mg).[12] In another work, Ingold and co-workers depicted the synthesis of *R*,*R*,*R*-d_2-γ-tocopherol in four steps from γ-tocopherol itself.[13] Though this last route proceeds in good yields, the high cost and the very low commercial availability of the starting material, the natural γ-tocopherol, make it expensive and hardly scalable. In this paper, we report a very efficient route for the preparation of trideuterated *R*,*R*,*R*-γ-tocopherol **11** from the cheap natural δ-tocopherol. The same protocol is also very convenient for large scale synthesis of unlabeled *R*,*R*,*R*-γ-tocopherol, starting from inexpensive and widely available *R*,*R*,*R*-α-tocopherol.

2. Results and discussion

In designing a route to γ-tocopherol labeled with deuterium atoms, different positions can be chosen on the basis of synthetic considerations, the reason of labeling and the analytical techniques to be used for its detection. In the last years, several ESI and APCI LC-MS/MS analytical methods

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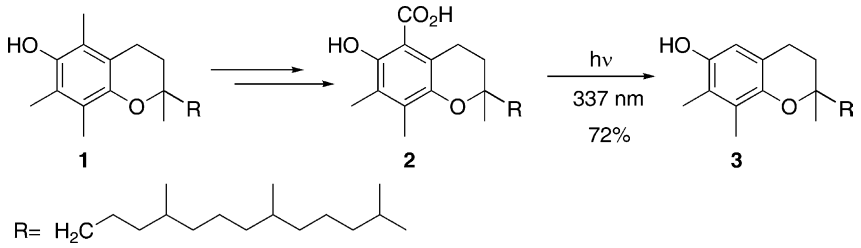


Figure 1. Transformation of α- into γ-tocopherol through photodecarboxylation of **2**.[15]

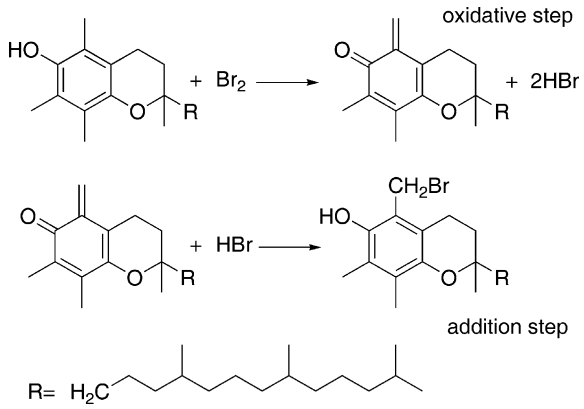
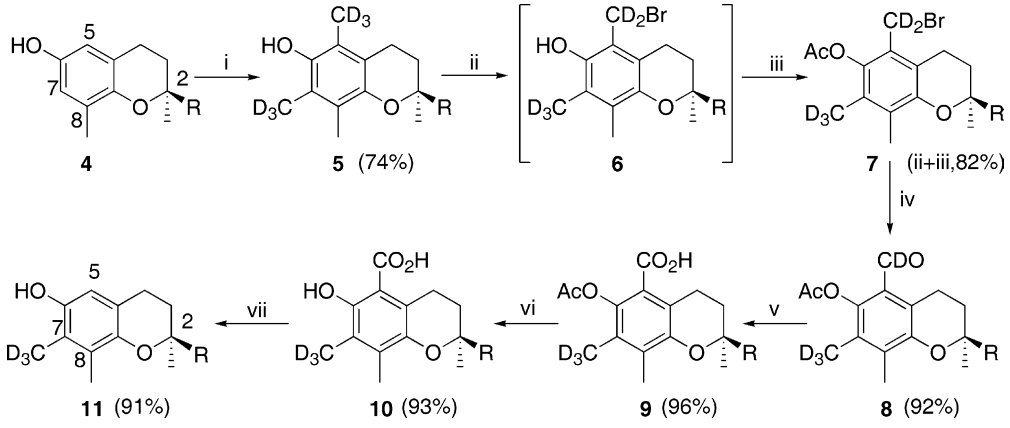


Figure 2. Proposed reaction mechanism of the bromination of α-tocopherol.[17]

have been developed successfully for tocopherols determination in various matrices, employing deuterated tocopherols as internal standards.[8–10] These results made LC-MS/MS the technique of choice for this kind of study. We planned to introduce labeling as CD_3 on one of the methyl groups of the aromatic ring, considering the degradation metabolic pathway of γ-tocopherol that results in γ-CEHC formation, that is, without modification of the chromanol ring.[14] In this way, interference of natural isotopes of the analyte on the *m/z* value of the labeled compound is avoided and d_3-γ-CEHC metabolite coming from supplementation can be traced.

Basically, two routes can be conceived for the synthesis of enantiopure labeled γ-tocopherol. One approach involves designing a suitable way for the preparation of labeled 2,3-dimethylhydroquinone, followed by the subsequent building of the chroman ring and aliphatic side chain in a stereoselective manner. In the other approach, convenient transformations without loss of enantiopurity have to be devised to introduce labeling directly on readily accessible chiral tocopherols, such as the natural ones, or their derivatives. According to Rosenau and Habicher,[15] it is possible to prepare γ-tocopherol starting from α-tocopherol through a multi-step procedure, the key point being photodecarboxylation of γ-tocopherol-5-carboxylic acid **2** (Fig. 1). Therefore, following this approach, we first prepared *R,R,R*-(5,7-$(CD_3)_2$)-α-tocopherol **5** as the precursor of the desired d_3-γ-tocopherol, introducing deuterium by $SnCl_2$-catalyzed deuteromethylation,[16] using $(CD_2O)_n$ on commercially available natural δ-tocopherol **4**. Bromination of **5** gave d_5-5-bromomethyl-γ-tocopherol **6** in almost quantitative yields.[17] According to the proposed mechanism, α-tocopherol oxidation leads to the *ortho*-quinone methide species, which adds hydrogen bromide formed in the first step, affording the benzylic brominated product (Fig. 2).

Before oxidizing the benzylic function, the phenolic hydroxyl group had to be protected in order to avoid its oxidation and relative by-products formation. Therefore, after evaporation of the solvent, acetylation was performed in the same flask under acid-catalyzed mild conditions. This prevents HBr elimination from **6**, which is highly susceptible to oxidation, bases and temperatures above 50 °C. Elimination of HBr would lead to an *ortho*-quinone methide intermediate and formation of α-tocopherol spirodimer. The acetylated product **7** was then oxidized



Scheme 1. Synthesis of *R,R,R*-(7-$^2H_3$)-γ-tocopherol **11**. (i) *i*-Pr_2O, $SnCl_2$, $(CD_2O)_n$, DCl in D_2O, 65 °C, 4 h; (ii) Br_2 in hexane, rt, 3 h; (iii) Ac_2O, AcOH, CH_2Cl_2, H_2SO_4 cat., rt, overnight; (iv) NMMO, 4 equiv, acetonitrile, rt, overnight; (v) NH_2SO_3H, $NaClO_2$ in 1,4-dioxane/H_2O, rt, 50 min; (vi) KOH 2 M in MeOH, 50 °C, 2 h; (vii) heating at 170 °C, 3 h.

following a different procedure from the one reported in literature.[15] In our hands, $KMnO_4$ oxidation under phase-transfer catalysis proved to be rather tedious and low yielding because of the difficulties encountered in the purification step. Therefore, we prepared the desired acid derivative **9** through a two steps oxidation. First, benzylic bromide **7** was reacted with anhydrous *N*-methylmorpholine-*N*-oxide (NMMO) to give aldehyde **8** in 92%, and then **8** was treated with $NH_2SO_3H/NaClO_2$ mixture, affording the acid **10**, after the saponification, in 90% overall yield from **7** (Scheme 1).

It has been reported that γ-tocopherol-5-carboxylic acid undergoes photodecarboxylation through a radical mechanism in an average yield of 72% upon irradiation at 337 nm, in the presence of iron complexes or activated titanium dioxide (Fig. 1).[15] Experiments carried out with radical starters, such as AIBN, gave only radicals coupling products, showing that only the photochemically excited form of γ-tocopherol-5-carboxylic acid is able to stabilize itself by decarboxylation. Photoirradiation requires special equipment not available in many synthetic laboratories. Therefore, we looked for an alternative procedure to remove the carboxylic group. The decarboxylation of aromatic acids is most often carried out by heating with quinoline and copper or copper salts,[18] but heating the salt of the acid[19] or the acid in an acidic medium has also been used with certain substrates.[20,21]Before trying one of those methods, we first performed a set of experiments simply heating the unlabeled compound **13** (prepared from *R*,*R*,*R*-α-tocopherol as described for its labeled counterpart, Scheme 2) under inert atmosphere. While keeping **13** at 150 °C for 3 h gave a small conversion of the acid into the desired product **14**, carrying out the thermal decarboxylation at 200 °C resulted in almost complete conversion of the acid **13**, allowing us to recover γ-tocopherol **14** in 65% yield, comparable to the yield reported using photodecarboxylation.[15] Therefore, considering these results, we performed a tuning of the reaction temperature, which showed that 170 °C was the best compromise between conversion and by-product formation. Under these conditions, both **11** and **14** were obtained with an excellent 91% yield, respectively, from **10** and **13**. Analyses carried out by chiral HPLC on a Chiracel OD-H Daicel column showed that no epimerization at the C-2 chiral center occurred throughout the synthesis, thus assessing that the *R*,*R*,*R* configuration of the starting δ- and α-tocopherol were retained. From all our experience, it can be assumed that no erosion of stereochemistry of the aliphatic side chain took place under the reaction conditions. Moreover, isotope purity of **11** was highly satisfying, resulting 97.6% by GC-MS.

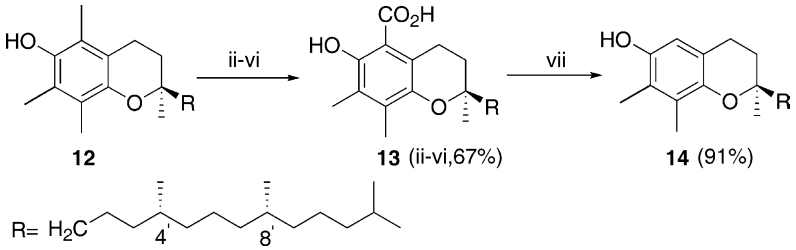
3. Conclusions

Over the last few years focus of vitamin E research has shifted significantly from the well-known bioactivity of α-tocopherol to the less investigated properties of other tocopherols and tocopherol derivatives, which have been proving very important. The high costs of commercially available γ-tocopherol and the difficulty of preparing its labeled analogue have somewhat limited the studies on this very interesting compound. For this reason, we set up an efficient, simple and scalable route that allows the preparation of d_3-*R*,*R*,*R*-γ-tocopherol and *R*,*R*,*R*-γ-tocopherol starting, respectively, from inexpensive and widely available natural δ-tocopherol and *R*,*R*,*R*-α-tocopherol. The simple thermal decarboxylation of the final step afforded the desired product in excellent yields and without loss of isomeric purity, greatly improving the previous reported procedure.

4. Experimental

4.1. General

All reactions were performed under inert atmosphere (Ar or N_2). ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 spectrometer (200 and 50.3 MHz, respectively). ^2H NMR spectra were recorded on a Varian VXR 300 spectrometer (46 MHz for ^2H) in $CHCl_3$ with $CDCl_3$ as internal standard. Chemical shifts are expressed on the δ scale (ppm). Deuteration level was determined by GC-MS by microSIS mode. GC-MS analyses were recorded on a Saturn 2000 GC-MS/MS Varian Chromatography System mass spectrometer connected to a 3800 Varian gas chromatograph equipped with a DB-5 capillary column (30 m×0.25 mm, 0.25 μm film thickness). Operating conditions: injector temperature 280 °C; oven program temperature 250 °C, increased at 30° min^{-1} to 300 °C and held for 7 min at 300 °C; transfer line temperature 295 °C; ion trap temperature 250 °C; emission current 10 μA; isolation window 3 amu. The APCI mass spectra were acquired on an Applied Biosystem API 4000 mass spectrometer. HPLC analyses for determination of the isomeric purity were performed on a 250×4.6 mm Chiracel OD-H column from Daicel Chem. Ind., solvent 0.5% EtOH in *n*-hexane, flow 1.0 mL/min, detection at 220 nm, using *R*,*R*,*R*- and (all-*rac*)-γ-tocopherol as standards. Commercial reagents and solvents were purchased from Aldrich, Fluka, or Merck, and purified by standard methods when necessary. Hexane was distilled over CaH_2 before use, CH_2Cl_2 over P_2O_5, *i*-Pr_2O over Na. Deuterated paraformaldehyde $(CD_2O)_n$ (≥99.5 at.% D) and DCl in D_2O (35% in DCl, 99.9 at.%



Scheme 2. Synthesis of *R*,*R*,*R*-γ-tocopherol **14**. Reactions details are the same as Scheme 1.

D) were purchased from C/D/N Isotopes (Canada), whilst $NaBD_4$ (98 at.% D) and D_2O (99.8 at.% D) from Aldrich. 2*R*,4′*R*,8′*R*-α-Tocopherol (Covitol F1490) was purchased from Henkel. All other commercial reagents were used without further purification. Column chromatography was performed on silica gel 60 (70–230 mesh). TLC was performed on silica gel Macherey–Nagel Alugram Sil G/UV_{254} (0.20 mm). All yields given refer to isolated yields.

4.1.1. (5-$^2H_3$,7-$^2H_3$)-(2*R*,4′*R*,8′*R*)-α-tocopherol (5).[16] To a solution of natural δ-tocopherol (1.95 g, 4.72 mmol) in anhydrous *i*-Pr_2O (50 mL) were added anhydrous $SnCl_2$ (13.9 g, 73.3 mmol, 15.5 equiv), DCl in D_2O (50 g, 35%, 99.9% D) and $(CD_2O)_n$ (1.1 g, 34.3 mmol, 7.28 equiv). The mixture was heated at 65 °C for 4 h, and then water was added. The aqueous phase was extracted with Et_2O (3× 100 mL). The combined organic extracts were subsequently washed to neutrality with water, dried over Na_2SO_4 and concentrated to dryness. Purification by column chromatography (Hex/EtOAc 12:1) afforded **5** (1.52 g, 74% yield) as pale yellow oil.

^{1}H NMR, ($CDCl_3$/TMS): δ 0.7–1.6 (m, 36H, C(2a)H_3 and $C_{16}H_{33}$ chain), 1.8 (m, 2H, $ArCH_2CH_2$), 2.1 (s, 3H, $ArCH_3$), 2.6 (t, *J*=6.2 Hz, 2H, $ArCH_2CH_2$). ^{2}H NMR ($CHCl_3$): δ 2.09 (s, 3D, $ArCD_3$), 2.13 (s, 3D, $ArCD_3$). ^{13}C NMR ($CDCl_3$): δ 10–11.1 (m), 11.7, 19.6, 19.7, 20.7, 21.03, 22.6, 22.7, 23.8, 24.4, 24.8, 27.9, 30.8, 31.6, 32.7, 32.8, 37.3, 37.4, 37.5, 39.4, 39.8, 74.5, 117.4, 118.4, 120.9, 122.6, 144.6, 145.6. APCI-MS (in MeOH), *m*/*z* (amu): positive ion mode, 437.6 $[M]^+$.

4.1.2. 6-*O*-Acetyl-5-(5-$^2H_2$)-bromomethyl-(7-$^2H_3$)-(2*R*,4′*R*,8′*R*)-γ-tocopherol (7). To a solution of **5** (1.38 g, 3.16 mmol) in dry hexane (25 mL) was added dropwise a solution of Br_2 (0.17 mL, 3.32 mmol, 1.05 equiv) in dry hexane (10 mL). The solution was stirred for 3 h. The solvent and the remaining Br_2 were removed in vacuo at rt, affording **6** without further purification. ^{1}H NMR of **6** was consistent with reported data.[17] In the same flask was then carried out the acetylation reaction to prepare **7**. To **6**, obtained as described above, were added CH_2Cl_2 (12 mL), AcOH (12 mL), Ac_2O (2.2 mL) and H_2SO_4 (0.2 mL). The dark mixture was stirred overnight at rt. Then water was added and CH_2Cl_2 evaporated. The aqueous phase was extracted with hexane (3×100 mL). The combined organic extracts were subsequently washed to neutrality with water, dried over Na_2SO_4 and concentrated to dryness. Purification by column chromatography (Hex/EtOAc 10:1) afforded **7** (1.45 g, 82% yield from **5**) as yellow dense oil.

^{1}H NMR, ($CDCl_3$/TMS): δ 0.95–1.8 (m, 36H, C(2a)H_3 and $C_{16}H_{33}$ chain), 1.8 (m, 2H, $ArCH_2CH_2$), 2.1 (s, 3H, $ArCH_3$), 2.37 (s, 3H, CH_3CO_2), 2.75 (t, *J*=6.6 Hz, 2H, $ArCH_2CH_2$). ^{2}H NMR ($CHCl_3$): δ 1.94 (s, 3D, $ArCD_3$), 4.36 (s, 2D, $ArCD_2Br$). $C_{31}H_{46}D_5BrO_3$ (490.7): calcd C 66.89, H 10.14, Br 14.35, found C 66.65, H 10.35, Br 14.48.

4.1.3. 6-*O*-Acetyl-5-(5-$^2H_1$)-formyl-(7-$^2H_3$)-(2*R*,4′*R*,8′*R*)-γ-tocopherol (8). To a solution of **7** (1.34 g, 2.41 mmol) in dry acetonitrile (20 mL), NMMO (1.14 g, 9.7 mmol, 4 equiv) was added. After stirring for 5 h at rt, the solvent was evaporated and the crude residue purified by column chromatography (Hex/EtOAc 15:1), affording **8** (1.17 g, 92% yield) as yellow dense oil.

^{1}H NMR, ($CDCl_3$/TMS): δ 0.95–1.6 (m, 36H, C(2a)H_3 and $C_{16}H_{33}$ chain), 1.7 (m, 2H, $ArCH_2CH_2$), 2.1 (s, 3H, $ArCH_3$), 2.3 (s, 3H, CH_3CO), 3.05 (t, *J*=6.2 Hz, 2H, $ArCH_2CH_2$). ^{2}H NMR ($CHCl_3$): δ 2.01 (s, 3D, $ArCD_3$), 10.25 (s, 1D, ArCDO). ^{13}C NMR ($CDCl_3$): δ 12.9, 13.01 (m), 19.6, 19.7, 20.4, 20.9, 22.5, 22.6, 23.8, 24.7, 27.9, 30.5, 30.7, 32.6, 32.7, 37.2, 37.3, 37.4, 39.3, 39.9, 75.8, 120.5, 122.8, 128.2, 136.6, 145.0, 149.8, 169.6, 189.9 (t, *J*=105 Hz). APCI-MS (in MeOH), *m*/*z* (amu): positive ion mode, 491.4 $[M+H]^+$, 508.6 $[M+NH_4]^+$. $C_{31}H_{46}D_4O_4$ (490.7): calcd C 75.87, H 11.09, found C 75.41, H 11.27.

4.1.4. 6-*O*-Acetyl-(7-$^2H_3$)-(2*R*,4′*R*,8′*R*)-γ-tocopherol-5-carboxylic acid (9). To a solution of **8** (490 mg, 1 mmol) in 1,4-dioxane (20 mL), NH_2SO_3H (160 mg, 1.6 mmol, 1.6 equiv) and water (7 mL) were added. After stirring for 20 min, $NaClO_2$ (180 mg, 1.4 mmol, 1.4 equiv) and water (5 mL) were added. After stirring for further 30 min, Na_2SO_3 (150 mg) was added to destroy excess of $NaClO_2$ and HOCl formed during the reaction. Water was then added and the aqueous phase was extracted with Et_2O (3× 50 mL). The combined organic extracts were subsequently washed to neutrality with water, dried over Na_2SO_4 and concentrated to dryness, giving pure **9** (485 mg, 96% yield) without further purification, as yellow oil.

^{1}H NMR, ($CDCl_3$/TMS): δ 0.95–1.6 (m, 36H, C(2a)H_3 and $C_{16}H_{33}$ chain), 1.7 (m, 2H, $ArCH_2CH_2$), 2.1 (s, 3H, $ArCH_3$), 2.28 (s, 3H, CH_3CO), 2.9 (t, *J*=6.2 Hz, 2H, $ArCH_2CH_2$), 9.2 (bs, 1H, CO_2H). ^{2}H NMR ($CHCl_3$): δ 2.01 (s, $ArCD_3$). ^{13}C NMR ($CDCl_3$): δ 12.8, 12.9 (m), 19.6, 19.7, 20.6, 21.1, 22.5, 22.7, 24, 24.4, 24.7, 27.9, 30.6, 32.7, 37.2, 37.3, 39.3, 40.1, 76, 118.3, 121.5, 128.9, 130.3, 140.5, 150, 170.1, 171.9. APCI-MS (in MeOH), *m*/*z* (amu): negative ion mode, 504.5 $[M-H]^-$. $C_{31}H_{47}D_3O_5$ (505.7): calcd C 73.62, H 10.56, found C 73.25, H 10.85.

4.1.5. (7-$^2H_3$)-(2*R*,4′*R*,8′*R*)-γ-tocopherol-5-carboxylic acid (10). To **9** (490 mg, 0.97 mmol) was added a solution of KOH in MeOH (10 mL, 2 M). The solution was heated at 50 °C for 2 h, then MeOH was evaporated and water added. The aqueous phase was extracted with Et_2O (3×50 mL). The combined organic extracts were subsequently washed to neutrality with water, dried over Na_2SO_4 and concentrated to dryness, giving pure **10** (420 mg, 93% yield) without further purification, as yellow semi-solid.

^{1}H NMR, ($CDCl_3$/TMS): δ 0.95–1.6 (m, 36H, C(2a)H_3 and $C_{16}H_{33}$ chain), 1.7 (m, 2H, $ArCH_2CH_2$), 2.1 (s, 3H, $ArCH_3$), 3.05 (t, *J*=6.2 Hz, 2H, $ArCH_2CH_2$), 9.8 (bs, 1H, ArOH), 11.1 (bs, 1H, CO_2H). ^{2}H NMR ($CHCl_3$): δ 2.01 (s, $ArCD_3$). ^{13}C NMR ($CDCl_3$): δ 11.8, 13.0 (m), 19.6, 19.7, 20.9, 22.6, 22.7, 23.6, 24, 24.4, 24.8, 27.9, 30.9, 31.4, 32.6, 32.8, 37.2, 37.3, 37.4, 39.3, 39.6, 74.6, 106.7, 119, 124, 136.1, 144.8, 155.9, 176.8. APCI-MS (in MeOH), *m*/*z* (amu): negative ion mode, 462.6 $[M-H]^-$. $C_{29}H_{45}D_3O_4$ (463.7): calcd C 75.11, H 11.08, found C 75.01, H 11.21.

4.1.6. (7-$^2H_3$)-(2*R*,4′*R*,8′*R*)-γ-tocopherol (11). Compound **10** (300 mg, 0.65 mmol) was heated at 170 °C for 3 h. After

purification of the crude residue by column chromatography (Hex/EtOAc 10:1), **11** (248 mg, 91% yield) was obtained as brown dense oil.

^{1}H NMR, ($CDCl_3$/TMS): δ 0.8–1.6 (m, 36H, C(2a)H_3 and $C_{16}H_{33}$ chain), 1.7 (m, 2H, ArCH$_2$CH_2), 2.1 (s, 3H, ArCH_3), 2.7 (t, J=6.2 Hz, 2H, ArCH_2CH$_2$), 4.7 (bs, 1H, ArOH), 6.4 (s, 1H, ArH). ^{2}H NMR ($CHCl_3$): δ 2.15 (s, ArCD_3). ^{13}C NMR ($CDCl_3$): δ 11.9 (m), 19.7, 19.8, 21.1, 22.3, 22.6, 22.7, 24, 24.4, 24.8, 27.9, 31.4, 32.7, 32.8, 37.3, 37.4, 37.45, 37.6, 39.4, 40, 40.1, 75.5, 112.2, 118.3, 121.7, 125.8, 145.7, 146.2. APCI-MS (in MeOH), *m/z* (amu): positive ion mode, 419.3 $[M]^+$. $C_{28}H_{45}D_3O_2$ (419.4): calcd C 80.13, H 12.25, found C 80.32, H 12.40. 97.6% deuteration by GC-MS (d_3 species; the remaining 2.4% accounts for d_2, d_1 and d_0 species). HPLC: 100% 2*R*-isomers (t(*R*) 16.1 min), no trace of 2*S*-isomers (t(*R*) 17.1 min) could be detected. It can be assumed that no erosion of stereochemistry of the aliphatic side chain took place under the reaction conditions.

4.1.7. (2*R*,4′*R*,8′*R*)-γ-tocopherol (14). Acid **13** was prepared as described for its labeled counterpart **10** starting from commercially available *R*,*R*,*R*-α-tocopherol. Thermal decarboxylation of **13** was accomplished (91% yield) as described for **11**. Physical and spectroscopic data were consistent with reported data for (2*R*,4′*R*,8′*R*)-γ-tocopherol.[22]

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References and notes

1. IUPAC-IUB *Eur. J. Biochem.* **1982**, *123*, 473–475.
2. Bunyan, J.; McHale, D.; Green, J.; Marcinkiewicz, S. *Br. J. Nutr.* **1961**, *15*, 253–257.
3. Weiser, H.; Vecchi, M.; Schlachter, M. *Int. J. Vit. Nutr. Res.* **1986**, *56*, 45–56.
4. Weiser, H.; Riss, G.; Kormann, A. W. *J. Nutr.* **1996**, *126*, 2539–2549.
5. Jiang, Q.; Christen, S.; Shigenaga, M. K.; Ames, B. N. *Am. J. Clin. Nutr.* **2001**, *74*, 714–722.
6. Hensley, K.; Benaksas, E. J.; Bolli, R.; Comp, P.; Grammas, P.; Hamdheydari, L.; Mou, S.; Pye, Q. N.; Stoddard, M. F.; Wallis, G.; Williamson, K. S.; West, M.; Wechter, W. J.; Floyd, R. A. *Free Radic. Biol. Med.* **2004**, *36*, 1–15.
7. Kayden, H. J.; Traber, M. G. *J. Lipid Res.* **1993**, *34*, 343–358.
8. Lauridsen, C.; Leonard, S. W.; Griffin, D. A.; Liebler, D. C.; McClure, T. D.; Traber, M. G. *Anal. Biochem.* **2001**, *289*, 89–95.
9. Mottier, P.; Gremaud, E.; Guy, P. A.; Turesky, R. J. *Anal. Biochem.* **2002**, *301*, 128–135.
10. Andreoli, R.; Manini, P.; Poli, D.; Bergamaschi, E.; Mutti, A.; Niessen, W. M. A. *Anal. Biochem.* **2004**, *378*, 987–994.
11. Stocker, A.; Rüttimann, A.; Woggon, W.-D. *Helv. Chim. Acta* **1993**, *76*, 1729–1738.
12. Stocker, A.; Netscher, Th.; Rüttimann, A.; Müller, R. K.; Schneider, H.; Todaro, L. J.; Derungs, G.; Woggon, W.-D. *Helv. Chim. Acta* **1994**, *77*, 1721–1737.
13. Hughes, L.; Slaby, M.; Burton, G. W.; Ingold, K. U. *J. Labelled Compd Radiopharm.* **1990**, *28*, 1049–1057.
14. Wechter, W. J.; Kantoci, D.; Murray, E. D. J.; D'Amico, D. C.; Jung, M. E.; Wang, W. H. *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 6002–6007.
15. Rosenau, Th.; Habicher, W. D. *Synlett* **1997**, *2*, 208–209.
16. Ingold, K. U.; Hughes, L.; Slaby, M.; Burton, G. W. *J. Labelled Compd. Radiopharm.* **1986**, *24*, 817–831.
17. Rosenau, Th.; Habicher, W. D. *Tetrahedron* **1995**, *51*, 7919–7926.
18. Cohen, T.; Schambach, R. A. *J. Am. Chem. Soc.* **1970**, *92*, 3189–3190.
19. Segura, P.; Bunnett, J. F.; Villanova, L. *J. Org. Chem.* **1985**, *50*, 1041–1045.
20. Huang, H. H.; Long, F. A. *J. Am. Chem. Soc.* **1969**, *91*, 2872–2875.
21. Kaeding, W. W. *J. Org. Chem.* **1964**, *29*, 2556–2559.
22. See references citation in: Baldenius, K. U.; von dem Bussche-Hünnefeld, L.; Hilgemann, E.; Hoppe, P.; Stürmer, R. In *Ullmann's Encyclopedia of Industrial Chemistry*, VCH Verlagsgesellschaft: Weinheim, 1996; Vol. A27, pp 478–488.