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Tocopherols by Hydride Reduction of Dialkylamino Derivatives

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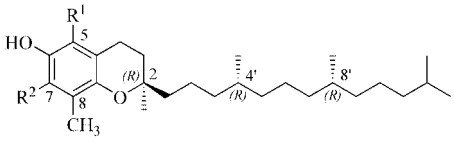
Aminomethylation with Mannich reagents derived from secondary amines and paraformaldehyde under improved conditions has been used to convert non-α-tocopherol homologues into α-tocopherol, the biologically most important vitamin E compound. Mono- and bis(aminomethylated) β-, γ- and δ-tocopherol were then subsequently transformed into the corresponding tocopherols (α- and β-tocopherol) by reductive deamination. As an alternative to classical catalytic hydrogenation in the last step, efficient laboratory protocols using complex hydrides have been derived and applied to the preparation of labelled vitamin E compounds.

Introduction

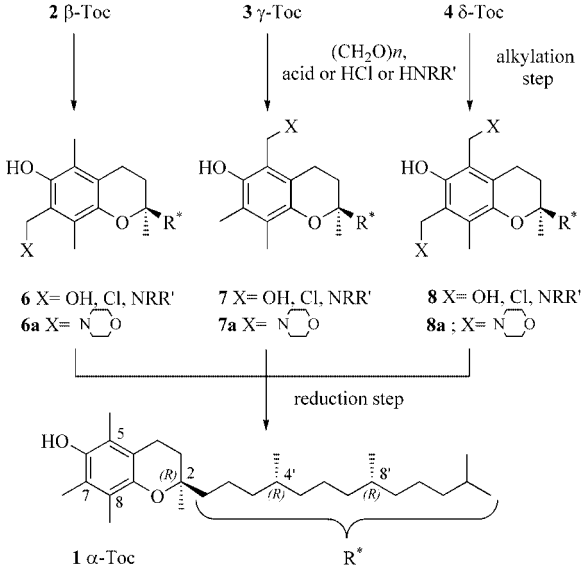
Tocopherols play an essential role in biological systems owing to their vitamin E and antioxidant activities.[1] All-racemic α-tocopherol, an equimolar mixture of eight stereoisomers prepared by acid-catalyzed condensation of trimethylhydroquinone and racemic isophytol, is the product of highest economic relevance.[2] The naturally occurring (2*R*,4′*R*,8′*R*)-α-tocopherol (**1**) can be obtained on an industrial scale from the processing of natural material. However, in most sources used for this purpose, for example, soybeans and sunflowers, **1** is accompanied by the lower homologues, β-, γ- and δ-tocopherol (**2**–**4**, Figure 1), which possess lower vitamin E activity. Therefore, improvement of the chemical conversion of **2**–**4** into **1** is an attractive goal.



$R^1 = CH_3$, $R^2 = CH_3$ α-tocopherol, **1**
$R^1 = CH_3$, $R^2 = H$ β-tocopherol, **2**
$R^1 = H$, $R^2 = CH_3$ γ-tocopherol, **3**
$R^1 = H$, $R^2 = H$ δ-tocopherol, **4**

Figure 1. Naturally occurring tocopherols.

Generally, two-step alkylation/reduction sequences are used for this transformation, including halo-,[3] amino-,[4] and hydroxymethylation reactions[5] (Scheme 1), but most of them suffer from disadvantages relating to the selectivity of the reactions and the reagents and reaction conditions used. We previously disclosed our results on the efficient preparation of **1** from lower homologues using a hydroxymethylation/hydrogenation[6] sequence in the presence of boric acid.



Scheme 1. Two-step alkylation/reduction sequence generally used in the conversion of non-α-tocopherols into **1**.[7]

For the aminomethylation route, it is known from the literature[4,7] that conversion of tocopherol mixtures of **2**–**4** into the corresponding aminomethyl derivatives is incomplete. The catalytic hydrogenation reaction, performed subsequently to convert the incompletely aminomethylated

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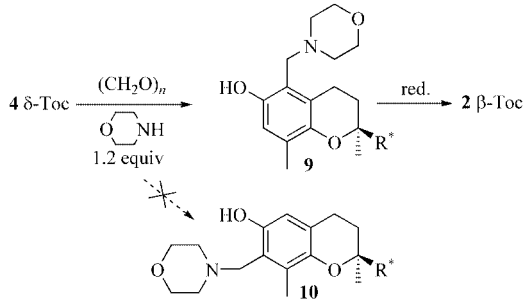
product mixture into **1**, leads to a mixture containing lower tocopherol homologues that then has to undergo an additional reaction cycle of aminomethylation/catalytic reduction for complete conversion into **1**. This drawback has been solved through the application of a protocol developed in our laboratories for efficient aminomethylation of vitamin E concentrates (Scheme 1).[7] Herein we report an exhaustive study of the reductive deamination step carried out with complex hydrides, an alternative to the classic hydrogenation protocol. The deamination procedure disclosed is particularly useful for the preparation of selectively labelled vitamin E analogues, as effective as previously reported by using $NaCNBD_3$.[8]

Results and Discussion

Efficient procedures for aminomethylation using Mannich reagents have been developed in our laboratories (Scheme 1).[7] The reagents can be prepared easily from paraformaldehyde and secondary dialkylamines, for example, diethylamine, morpholine (preferred) or piperidine, in a 1:1 ratio. Best results are obtained when the alkylation step is carried out under solvent-free conditions at temperatures of 80–140 °C over several hours. Complete alkylation, including double alkylation of δ-tocopherol (**4**), can be achieved by using 4–10 mol-equiv. of Mannich reagent. If the aim is selective monoalkylation (vide infra, for the preparation of β-tocopherol, **2**), or if more expensive labelled formaldehyde has to be used, the amount of reagent can be reduced accordingly, while adapting the reaction conditions (temperature and time). Details of the alkylation of β-, γ- and δ-tocopherol (**2**–**4**) and subsequent standard catalytic hydrogenation, are specified in the Experimental Section.

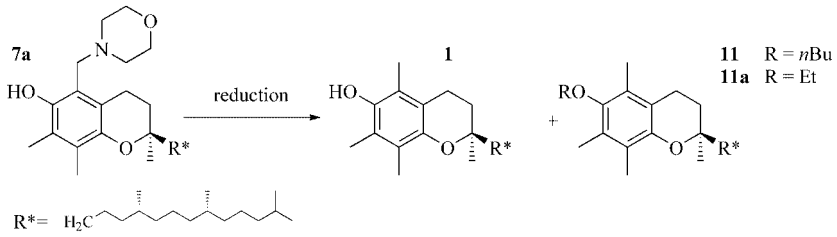
In addition to the complete double alkylation of the aromatic moiety (Scheme 1, **4** → **8**), being essential for the preparation of **1** in high yields, the protocol devised also allowed the highly regioselective monoalkylation **4** → **9** (Scheme 2), which represents a particular advantage of this approach in the efficient synthesis of β-tocopherol (**2**). In fact, by using roughly a stoichiometric amount of the Mannich reagent (1–1.2 equiv.) and by taking advantage of the different reactivity of the 5-position of **4** compared with the 7-position, it was possible to obtain **9** regioselectively in high yields (83%), which was then reduced (by catalytic hydrogenation or hydride treatment) to afford **2** quantitatively.



Scheme 2. Regioselective preparation of **2** from **4**.

In order to find an alternative deamination process without the use of catalytic hydrogenation for laboratory-scale preparations and, in particular, for the synthesis of labelled analogues, we carried out a series of experiments testing several reducing agents (mainly complex hydrides) in the transformation of **7a** into **1** (Table 1). The course of the reactions was monitored both by GC and HPLC analyses. The reagents used in Entries 1–11 gave essentially no or very little conversion into **1**. Moderate (Entry 12) to good yields (Entries 13 and 14) were obtained by acylation of the phenolic hydroxy function followed by quaternization of the amino group, thus transforming it into a better leaving group facilitating the subsequent reaction with the reducing agent. However, we continued our investigations by looking for an easier one-step reduction protocol. Therefore, several hydrides were investigated (Table 1, 4.5–5 equiv. of hydride used in all the experiments). $LiAlH_4$ led to only decomposition of the starting material **7a**, while no reaction occurred with DIBAH and BH_3. $Zn(BH_4)_2$, prepared in situ by treacing $ZnCl_2$ with $NaBH_4$ in THF according to a reported procedure,[9] proved to be too reactive in alcoholic solvents, and even in *i*BuOH it was consumed quickly. Changing the solvent to an aprotic medium like 1,4-dioxane afforded no α-tocopherol, while TLC and HPLC analyses showed the formation of a moderate amount of an unknown compound. Excess *n*PrOH was then added to a sample of the reaction mixture which was then refluxed for 2 h, showing complete disappearance of the unknown compound and the presence of starting material only. We then supposed that the observed compound was a complex formed between $Zn(BH_4)_2$ and **7a**, maybe favoured by the coordinating solvent. A similar behaviour was observed using $LiBH_4$[10] in THF, with the formation of the supposed hydride–**7a** complex in up to 80% yield without any appreciable conversion into α-tocopherol. Addition of a few millilitres of *n*PrOH to the reaction mixture also gave the starting material quantitatively after 2 h reflux. $LiBH_4$ was slightly more resistant to hydrolysis in *i*BuOH than $Zn(BH_4)_2$, affording **1** in 20% yield after 6 h. While $NaBH(AcO)_3$ proved to be ineffective (Entry 23), the use of $NaBH_4$ in polar solvents gave interesting results. The use of diglyme and DMF provided low and moderate yields, respectively, accompanied by decomposition of **7a**, whereas reactions carried out in DMSO (Entry 26) afforded irreproducible data, although a yield of 86% was obtained in one experiment, and are also less practical in the workup. Better results were obtained by using alcoholic solvents (Entries 27–30, 35). Water was not tested because of the insolubility of the substrate in this solvent, while MeOH was avoided because of the rapid decomposition of $NaBH_4$ in this solvent.[11] Though such a decomposition is slower in EtOH, the yield of reduction of **7a** was no better than 50%. Increasing the reaction temperature by using alcoholic solvents with higher boiling points (Entries 28–30) led to a substantial improvement, with yields ranging from 64 to 90% when refluxing in *i*BuOH for 12 h. We observed the formation of a viscous white gel in the reaction medium which increased with temperature and time of reaction,

Table 1. Reduction trials for the transformation of **7a** into **1**.



Entry	Reagent	Solvent	Temp.	Time	Result[a]
1	Li	NH_3/THF	–80 °C → room temp.	2.5 h	only **7a**
2	Na	NH_3/THF	–80 °C → room temp.	16 h	mainly **7a** + dec.
3	Na	EtOH	reflux	22 h	**7a** (39%) + **11a**
4	Zn	AcOH	reflux	1.5 h	mainly **7a**
5	LiDBB	THF	room temp.	5 h	mainly **7a**
6	Ph_2PLi	THF	reflux	5 d	mainly **7a**
7	$TiCl_3$/Li	THF	reflux	3 d	**7a** (32%) + **1** (12%) + dec.
8	Ni/Al, KOH	H_2O	100 °C	5 h	only **7a**
9	HCOOH	CH_2Cl_2	reflux	16 h	only **7a**
10	$HSiCl_3$/Et_3N	CH_3CN	75 °C	16 h	mainly **7a**
11	Pd/C	HCO_2H/MeOH	room temp.	2 d	**7a** (23%) + **1** (12%) + n.i.
12	1. Ac_2O, 2. HCl, 3. $SnCl_2$				47% **1**
13	1. Ac_2O, 2. MeI/Ag^+, 3. $NaBH_3CN$				71% **1**
14	1. diphosgene/Hünig's base, 2. $LiAlH_4$				88% **1**
15	DIBAH	hexane	reflux	16 h	only **7a**
16	BH_3/THF	THF	room temp.	5 d	only **7a**
17	$ZnCl_2$+$NaBH_4$	1,4-dioxane	reflux	6 h	only **7a**
18	$ZnCl_2$+$NaBH_4$	*i*BuOH			mainly **7a**+ 7% **1**
19	$LiAlH_4$	THF	reflux	2 d	mainly dec.
20	$LiBH_4$	THF	reflux	12 h	only **7a**
21	$LiBH_4$	*i*BuOH	70 °C	6 h	**7a** + 20% **1**
22	$LiEt_3BH$	THF	reflux	2 d	only **7a**
23	$NaBH(AcO)_3$	THF	reflux	22.5 h	only **7a**
24	$NaBH_4$	diglyme	100 °C → 160 °C	7 h	mainly **7a** + dec.
25	$NaBH_4$	DMF	reflux	2 h	50% **1** + dec.
26	$NaBH_4$	DMSO	120 °C	6 h	max. 86% **1**
27	$NaBH_4$	EtOH	reflux	21 h	50% **1** + 50% **7a**
28	$NaBH_4$	*i*PrOH	reflux	2 d	50–60% **1** + 30–40% **7a**
29	$NaBH_4$	*t*BuOH	reflux	21 h	64% **1** + 36% **7a**
30	$NaBH_4$	*i*BuOH	reflux	12 h	90% **1** + 10% **7a**
31	$NaBH_3CN$	DMSO	120 °C	4.5 h	26% **1** + 37% **7a** + 9% n.i.
32	$NaBH_3CN$	EtOH	reflux	22 h	56% **1** + 17% **7a** + 5% n.i.
33	$NaBH_3CN$	*i*BuOH	reflux	4 h	95% **1**
34	Bu_4NBH_4	*i*BuOH	reflux	4 h	77% **1** + 19% **11**
35	$NaBH_4$/OH^-	*i*BuOH	reflux	10 h	ca. 100% **1**

[a] Qualitative results from screening experiments are given for the cases in which no (only **7a**) or low (mainly **7a**) conversion of **7a** or major decomposition (dec.) and formation of unknown compounds (n.i. not identified) occurred.

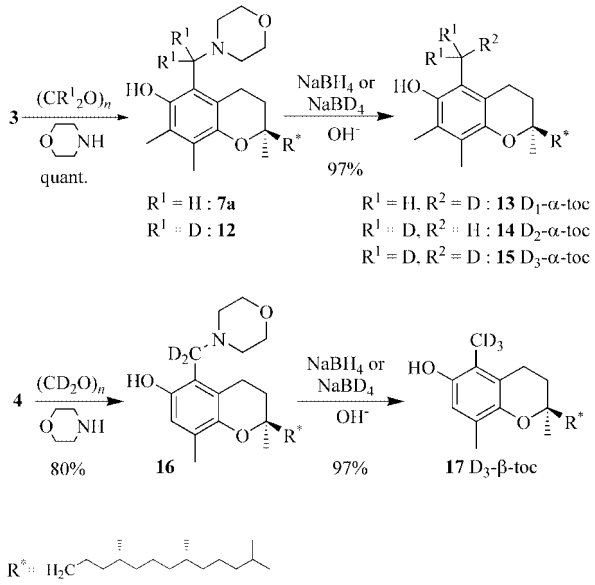
quite evident using *i*BuOH, and disappeared on addition of water. This behaviour was not observed by refluxing *i*BuOH and $NaBH_4$ together. Surprisingly, $NaCNBH_3$ gave better and reproducible results under these conditions after 4 h, affording **1** in almost quantitative yield (95%, Entry 33). Similar conversions were obtained by treating **7a** with Bu_4NBH_4 in refluxing *i*BuOH (Entry 34), the reaction medium remaining a homogeneous solution, but the desired α-tocopherol was accompanied by the formation of moderate amounts (15–25%) of the corresponding *n*-butyl ether **11**. Formation of the *n*-butyl ether of the aminomethylated precursor **7a** was not observed.

On the basis of the data gathered in this hydride screening, we carried out further experiments with the aim of improving the performances of the reactions with $NaBH_4$ and Bu_4NBH_4. It was noticed that conversion of **7a** into **1** in refluxing *i*BuOH proceeded relatively well in the first few hours (60–70% after 3 h) and then became slower and slower (80% max. after 9 h) and was accompanied by an increase in gel formation. Increasing the initial loading of $NaBH_4$ (up to 8 equiv.) produced only limited improvements in the early stages of the reaction (5–15%) without significant changes in the subsequent reaction pattern. We supposed that decomposition of $NaBH_4$ accounted for the observed behaviour and the different reactivity compared with $NaCNBH_3$ which is more resistant to hydrolysis.[12] Supporting this hypothesis, a trial performed starting with 2 equiv. of $NaBH_4$ and by adding 2 equiv. every 3 h showed

a rather constant conversion difference for each addition, eventually affording **1** in 96% yield after 18 h. Further evidence came from experiments carried out in the presence of NaOH. $NaBH_4$ decomposition has been reported to be significantly slower in basic aqueous and alcoholic solutions.[13] Indeed, reduction of **7a** in refluxing *i*BuOH using 5 equiv. of $NaBH_4$ (starting $[BH_4^-]$ = 0.6 M) and 2 equiv. of NaOH occurred to give 82% yield after 3 h and 96% yield after 6 h. Moreover, the same very good yields were obtained by using a three-fold lower starting concentration of $NaBH_4$ ($[BH_4^-]$ = 0.2, 4 equiv. $NaBH_4$, 2 equiv. NaOH) and complete conversion was reached in 9–10 h on addition of one more equivalent of $NaBH_4$ after 7 h. Using the same conditions in the analogous transformation of **9** into **2** provided β-tocopherol in quantitative yield in 10 h. Conversely, reduction of bis(morpholinomethylated) **8a** to α-tocopherol proceeded more slowly using this protocol, very likely due to the increased steric hindrance and to the different reactivity of the 5-position compared with the 7-position, as has been observed in several other cases.[14] In particular, after refluxing for 6 h, the resulting reaction mixture was composed of 5% **1**, 15% **7a**, 60% **6a** and 20% **8a**. The addition of 2 equiv. of $NaBH_4$ changed the composition to 26% **1**, 1–2% **7a**, 62% **6a** and 10% **8a** after 9 h of overall reflux. Further additions of hydride (11 equiv. total) allowed complete conversion of **8a**, but only 60% formation of **1** and 40% unreacted **6a**. The higher resistance of **6a** to hydride reduction compared with **7a** was also observed in the preparation of [C^7-^{13}C]-α-tocopherol from 7-(morpholino-[^{13}C]-methyl)-β-tocopherol using $NaCNBH_3$ (*i*BuOH reflux, 5 equiv., $[BH_3^-]$ = 0.8 M), in which the desired labelled α-tocopherol was recovered in 34% yield after 6 h together with the unreacted aminomethylated precursor.[15] These findings suggest that the hydride reduction proceeds through an *o*-quinomethide intermediate, with the 5-position being highly preferred over the 7-position, as reported previously.[14]

Interestingly, Bu_4NBH_4 provided the best hydride loading/conversion ratio, but we did not find reaction conditions to completely avoid the formation of *n*-butyl ether **11**. However, the ether can be easily separated from **1** by column chromatography [hexane/EtOAc, 8:1; R_f(**11**) = 0.78, R_f(**1**) = 0.51]. A lower temperature led to a longer reaction time and not less than 7–12% of **11**. Addition of small amounts of water (2–5%, starting $[BH_4^-]$ = 0.2 M) afforded the best result in terms of byproduct formation (**11**, 5%), but conversion was no higher than 86%. A similar result was obtained by refluxing in *n*PrOH instead of *i*BuOH. Using a lower initial loading of Bu_4NBH_4 (1 equiv., $[BH_4^-]$ = 0.05 M) provided 77% of **1** and 6% of **11** after 7 h. Addition of a further equivalent of Bu_4NBH_4 afforded almost quantitative conversion, yielding 84% of **1** and 14% of **11**.

While the reduction conditions outlined above give poorer performances than classic hydrogenation in the conversion of 7-(aminomethylated) vitamin E concentrates into α-tocopherol, they represent a very efficient procedure with which to prepare labelled (stable and unstable isotopes) α- and β-tocopherols[8b] and tocotrienols[8a] in association with the devised solvent-free aminomethylation protocol. By combining the use of deuteriated or unlabelled paraformaldehyde and $NaBH_4$ it is possible to prepare mono-, di- and trideuteriated analogues. In this way, [D_1]-, [D_2]-, [D_3]-α-tocopherol and [D_3]-β-tocopherol were successfully and easily prepared in high yields and isotopic purity (Scheme 3).



Scheme 3. Preparation of [D_1]-, [D_2]-, [D_3]-α-tocopherols and [D_3]-β-tocopherol.

Conclusions

Efficient protocols for the alkylation of the lower homologues β-, γ- and δ-tocopherol (**2**–**4**) by aminomethylation/reduction sequences are now available. Moreover, high regioselectivity was obtained in the reaction between δ-tocopherol and a stoichiometric amount of the aminomethylation reagent (Mannich reagent), providing an easy synthesis of β-tocopherol. An exhaustive hydride reduction screening study was carried out in order to find alternatives to classical hydrogenation for the conversion of aminomethylated derivatives into α-tocopherol. $NaCNBH_3$ and $NaBH_4$/NaOH in *i*BuOH proved to be very effective in the reduction of 5-(aminomethylated) γ-tocopherol, but less efficient than hydrogenation in the reduction of bis(aminomethylated) δ-tocopherol. However, the conditions identified for hydride reduction are useful in the laboratory-scale preparation of multi-fold labelled α- and β-tocopherol and tocotrienols, increasingly used for metabolic studies and accurate quantitative analytical methods, and represent a very efficient alternative to previously reported methods for the synthesis of labelled vitamin E derivatives.[16]

Experimental Section

General: All reactions were carried out under argon. Room temperature (room temp.) corresponds to 20–22 °C. All solvents were

of puriss. quality and purchased from Fluka, Merck or Aldrich and were used without further purification. Paradeuterioformaldehyde was obtained from CEA (France). Bu_4NBH_4 was prepared according to the procedure reported by Brändström et al.[17] To isolate γ-(**3**) and δ-tocopherol (**4**), we used tocopherol concentrate, "d-Mixed Tocopherols" from Bizen Chemical Co., Ltd., Kumayama, Akaiwa, Okayama 709-07 (Japan), containing 11.17% **1**, 1.27% **2**, 37.26% **3**, 23.74% **4** (GC, acetate derivatives) and δ-tocopherol (Sigma) containing 86.8% **4**, 3.7% **3**, <0.1% **1** (GC, acetate derivatives) as starting materials, according to the purification procedure described below. Column chromatography: SiO_2, Merck, particle size usually 0.063–0.2 mm, 0.04–0.063 mm where indicated, 0–0.2 bar Ar. TLC: silica gel plates, Merck, SiO_2 60 F_{254}. Substances were detected with UV (254/366 nm) and ammonium molybdate/$Ce(SO_4)_2$ in H_2O/H_2SO_4 with subsequent heating. Supercritical fluid chromatography (SFC): Instrument Lee Scientific, model 600 (Dionex, Salt Lake City, UT, USA), FID at 380 °C, fused silica capillary column with biphenyl-30, length 10 m, i.d. 50 μm, mobile phase CO_2, 100 °C, 0.2–0.75 g mL^{-1}. HPLC: Lichrosorb S 160, 5 μm and LUNA C18(2), 5 μm, 250 × 4.6 mm (Phenomenex), CH_3CN/MeOH (50:50) 1.5 mL min^{-1}, λ = 295 nm. Melting points (uncorrected): Büchi 510 apparatus. IR spectra: Nicolet 7199 FT-IR spectrometer. ^1H and ^{13}C NMR spectra: $CDCl_3$, chemical shifts expressed on the δ scale (ppm), TMS as internal standard, Bruker Spectrospin WM-250, BrukerAC 300, Bruker AM-400. EI-MS and ISP-MS: SSQ 7000 (Finnigan MAT), EI; API III (SCIEX Perkin-Elmer), ISP; API 300 (SCIEX Perkin-Elmer), ISP; MAT 95 (Finnigan MAT) spectrometer, ISP or EI; indication of characteristic peaks, *m*/*z* (%).

Analytical Procedures

Tocopherols 1–4: The chemical purity was determined by GLC of the acetate derivatives. Squalane (50.2 mg, Fluka, 99.6%), DMAP (10 mg), pyridine and acetic anhydride (0.5 mL each) were added at room temp. to **1**–**4** (100 mg). The mixture was allowed to stand for 15 min at room temp. and then 1 μL was injected into the GLC apparatus. Values are given as wt.-% and were determined by the internal standard method. GLC was conducted on a PS-086 capillary column. The optical purity of **1**–**4** was determined by GLC of the methyl ether derivative.[18]

Mono- and Bis(alkylaminomethyl)tocopherols 6–10

Chemical Purity via Trimethysilyl Ether Derivatives: Pyridine and *N*,*O*-bis(trimethylsilyl)trifluoroacetamide (BSTAF) (0.1 mL each) were added to a crude mixture of an aminomethylation reaction (10 μL) or a crude product **6**–**10** (ca. 10 μg). The mixture was heated at 90 °C for 1 min and then diluted with 3 parts of AcOEt. The resulting solution was used directly for GC analysis. The values are given as area-% of trimethylsilyl ether derivatives **6**–OTMS to **10**–OTMS. GLC: capillary column PS-086 unless stated otherwise.

Purification of Raw Materials

δ-Tocopherol (4): δ-Tocopherol concentrate (150 g, Sigma) was diluted with eluent (150 mL hexane/AcOEt, 88:12) and purified by chromatography (column dimension: 90/10.5 cm; flow: 40 mL min^{-1}, fractions were checked by TLC every 200 mL). Tocopherol **4** was obtained after 6.5 L. Concentration of the collected fractions and distillation in vacuo (178–185 °C, 0.035 mbar, bulb-to-bulb) afforded **4** (97.0 g) as a yellow oil. Purity 98.58% (GC, acetate derivative): TLC (hexane/AcOEt, 9:1), R_f(**4**) 0.24. Shifts and allocations were in accordance with results of Baker and Myers.[19] Stereochemical purity (GLC, methyl ether derivative): 100%.

γ-Tocopherol (3): "d-Mixed Tocopherols" (80 g, Bizen) were diluted with eluent (80 mL hexane/AcOEt, 88:12) and purified by chromatography as described for the purification of **4**. The desired fraction was obtained after 6 L. Concentration of the collected fractions and distillation in vacuo (185 °C, 0.035 mbar, bulb-to-bulb) afforded **3** (20.0 g) as a yellowish oil. Purity >99% (GC, acetate derivatives). TLC (hexane/AcOEt, 9:1), R_f(**3**) = 0.29. ^1H NMR spectral data are identical to published values.[19] Stereochemical purity (GLC, methyl ether derivative): 100%.

Mannich Reagent Derived from Morpholine: Paraformaldehyde (30.0 g, 1 mol) was added portionwise to morpholine (87.1 mL, 1 mol) while stirring at 70 °C over 20 min in such a manner that the temperature rose to a maximum of 80 °C. After stirring at 80 °C for an additional 2 h, the reaction finished with the formation of a colourless liquid. According to the ^1H NMR spectrum, the reagent contained morpholinomethanol (**A**), dimorpholinomethane (**B**) and minor amounts of other unidentified components. Characteristic data: ^1H NMR (400 MHz, $CDCl_3$): δ = 2.14 (s, 1 H, OH, **A**), 2.50 (t, *J* = 4.6 Hz, 8 H, NCH_2CH$_2$O, **B**), 2.68 (m, 4 H, NCH_2CH$_2$O, **A**), 2.91 (s, 2 H, NCH_2N, **B**), 3.71 (m, 12 H NCH$_2$CH_2O, **A** + **B**), 4.13 (s, 2 H, NCH_2OH, **A**) 4.24–4.98 (not allocated signals) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 49.76 (NCH$_2$CH$_2$O, **A**), 52.00 (NCH$_2$CH$_2$O, **B**), 66.81 (NCH$_2$CH$_2$O, **A**), 67.00 (NCH$_2$CH$_2$O, **B**), 81.65 (NCH$_2$N, **B**), 87.23 (NCH$_2$OH, **A**) ppm. Signals were assigned on the basis of ^{13}C,^1H COSY NMR investigations and comparison with ^{13}C and ^1H NMR spectroscopic data of pure **B**. ISP-MS: *m*/*z* (%) = 187.3 (6) [**B** + H]$^+$, 159.3 (12), 129.3 (40), 118.2 (100) [**A** + H]$^+$.

(2*R*,4′*R*,8′*R*)-7-(Morpholinomethyl)-β-tocopherol (6a): The Mannich reagent derived from morpholine (9.37 g, 80 mmol) was added to mechanically stirred **2** (8.4 g, 20 mmol) at room temp. Then the mixture was heated to 125 °C within about 15 min and became tarnished. After 1.5 h, the aminomethylation was complete [control by GC, silylated derivatives: t_r(**2**) = 5.91 min, t_r(**6a**) = 10.67 min]. After cooling to room temp., the mixture was diluted with TBME (250 mL) and washed with H_2O until the wash solution became neutral (about 5–6 times with 50 mL of H_2O each). The organic layer was dried with K_2CO_3. Removal of the solvent in vacuo afforded **6a** (9.89 g) as a yellowish oil. Purity 97.7% (GC, silylated derivative). For further characterization, **6a** (1 g) was dissolved in MeOH (25 mL). While stirring the solution and slowly cooling to 0 °C, **6a** was obtained as a colourless precipitate. The solid was filtered off and recrystallized from MeOH. Colourless crystals. M.p. 33–36 °C. IR (KBr): $\tilde{\nu}$ = 3438 (s), 2952 (vs, sh), 2926 (vs), 2867 (s, sh), 1622 (m), 1457 (vs), 1417 (s), 1377 (s), 1261 (vs), 1118 (vs, sh), 1109 (vs), 1064 (s), 1005 (m), 915 (m) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.83–1.65 (m, 36 H), 1.78 (m, 2 H), 2.1 (s, 6 H), 2.60 (m, 6 H), 3.69 (s, 2 H), 3.74 (m, 4 H), 10.63 (s, 1 H) ppm. EI-MS: *m*/*z* (%) = 515.5 (35) [M]$^{+\cdot}$, 428 (100) [M – C_4H_9NO]$^+$, 165 (45) [$C_{10}H_{13}O_2$]$^+$. $C_{33}H_{57}NO_3$ (515.82): calcd. C 76.84, H 11.14, N 2.72; found C 76.59, H 11.17, N 2.75. The crude residue can be purified by column chromatography (hexane/AcOEt, 8:1). Alternatively, **6a** can be converted into the corresponding hydrochloride (**6a**·HCl): **6a** (3.7 g, 6.7 mmol) was dissolved in TBME (250 mL) and gaseous HCl (180 mL, 7.5 mmol) was passed through the solution to yield a colourless precipitate. Removal of the solvent in vacuo and recrystallization of **6a**·HCl (0.5 g) from AcOEt (10 mL) afforded **6a**·HCl as colourless crystals in the form of druses. M.p. 152–161 °C. IR (KBr): $\tilde{\nu}$ = 3430 (s), 2952 (vs, sh), 2928 (vs), 2869 (s, sh), 1455 (vs), 1261 (s), 1120 (s) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.83–1.65 (m, 36 H), 1.79 (m, 2 H), 2.17 (s, 3 H), 2.20 (s, 3 H), 2.61 (t, *J* = 6.8 Hz, 2 H), 3.03 (m, 2 H), 3.44 (d, *J* = 11.7 Hz, 2 H), 3.92 (d, *J* = 13 Hz, 2 H), 4.28–4.42 (m, 4 H), 7.44 (s, 1 H), 11.30 (s, 1 H) ppm. ISP-MS: *m*/*z* (%) = 516.5 (100) [M – HCl + H]$^+$, 429.5 (6.5) [M – HCl – C_4H_9NO + H]$^+$.

$C_{33}H_{58}ClNO_3$ (552.28): calcd. C 71.77, H 10.59, Cl 6.42, N 2.54; found C 71.70, H 10.47, Cl 6.70, N 2.49. Addition of 5% aq. NaOH to **6a**·HCl followed by extraction with TMBE provided **6a** quantitatively.

(2*R*,4′*R*,8′*R*)-5-(Morpholinomethyl)-γ-tocopherol (7a): The Mannich reagent derived from morpholine (9.37 g, 80 mmol) was added to mechanically stirred **3** (8.4 g, 20 mmol) at room temp. While adding morpholine, the yellowish mixture became tarnished. Then the mixture was heated to 80 °C within 15 min. After 0.5 h, the aminomethylation was complete [control by GC, silylated derivative; t_R(**3**) = 5.94 min, t_R(**7a**) = 10.01 min]. Workup as described for **6a** afforded **7a** (11.1 g) as a faint yellowish oil forming colourless crystals at room temp., purity 97.9% (GC, silylated derivative). For further characterization, **7a** (1 g) was dissolved in MeOH (22 mL) and recrystallized while stirring the solution and slowly cooling to 0 °C, precipitating colourless crystals. M.p. 40–41 °C. IR (KBr): $\tilde{\nu}$ = 3444 (w), 2954 (vs, sh), 2927 (vs), 2861 (s, sh), 1461 (vs), 1420 (m), 1379 (m), 1328 (m), 1302 (m), 1265 (s), 1114 (vs), 994 (m), 912 (m), 867 (m) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.84–1.6 (m, 36 H), 1.76 (m, 2 H), 2.11 (s, 3 H), 2.14 (s, 3 H), 2.60 (m, 6 H), 3.64 (s, 2 H), 3.74 (m, 4 H), 10.59 (s, 1 H) ppm. EI-MS: *m*/*z* (%) = 515 (21) $[M]^{+\cdot}$, 428 (100) $[M - C_4H_9NO]^+$, 203 (26), 165 (26) $[C_{10}H_{13}O_2]^+$. $C_{33}H_{57}NO_3$ (515.82): calcd. C 76.84, H 11.14, N 2.72; found C 76.93, H 11.19, N 2.74. The crude residue can be purified by column chromatography (hexane/AcOEt, 8:1). Alternatively, **7a** can be converted into the corresponding hydrochloride as described for the synthesis of **6a**·HCl. Recrystallization of **7a**·HCl (0.5 g) from AcOEt (10 mL) afforded **7a**·HCl as colourless crystals in the form of druses. M.p. 164–166 °C. IR (KBr): $\tilde{\nu}$ = 3179 (m), 2954 (vs, sh), 2922 (vs), 2869 (s, sh), 2618 (m), 1461 (vs), 1429 (s, sh), 1379 (s), 1350 (m), 1342 (m, sh), 1295 (s), 11 74 (s), 11 30 (s), 1118 (s), 1091 (s), 1080 (s) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.82–1.66 (m, 36 H), 1.81 (t, *J* = 6.8 Hz, 2 H), 2.11 (s, 3 H), 2.22 (s, 3 H), 2.69 (t, *J* = 6.8 Hz, 2 H), 3.04 (m, 2 H), 3.42 (m, 2 H), 3.89 (m, 2 H), 4.23 (m, 2 H), 4.40 (m, 2 H), 7.35 (s, 1 H), 11.30 (s, 1 H) ppm. EI-MS: *m*/*z* (%) = 515.5 (24) $[M - HCl]^{+\cdot}$, 428.3 (100) $[M - HCl - C_4H_9NO]^+$, 203 (14), 165 (7) $[C_{10}H_{13}O_2]^+$. $C_{33}H_{58}ClNO_3$ (552.28): calcd. C 71.77, H 10.59, Cl 6.42, N 2.54; found C 71.71, H 10.69, Cl 6.52, N 2.57. Addition of 5% aq. NaOH to **7a**·HCl followed by extraction with TMBE provided **7a** quantitatively.

(2*R*,4′*R*,8′*R*)-5,7-Bis(morpholinomethyl)-δ-tocopherol (8a): The Mannich reagent derived from morpholine (37.5 g, 320 mmol) was added to mechanically stirred **4** (16.4 g, 40.8 mmol) at room temp. During the addition, the yellowish mixture became tarnished. Then the mixture was heated to 135 °C within about 60 min as described for the preparation of **6a**. After 6 h, the aminomethylation was complete [control by GC, silylated derivatives; t_r(**4**) = 5.37 min, t_r(**9**) = 9.03 min, t_r(**8a**) = 16.41 min]. Workup as described for **6a** afforded **8a** (24.5 g) as a yellowish oil. Purity 96.3% (GC, silylated derivative). IR (film): $\tilde{\nu}$ = 2926 (vs), 2852 (s, sh), 1466 (vs), 1378 (m), 1302 (m), 1222 (s), 1159 (m), 1119 (vs), 990 (m), 864 (m) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.70–1.64 (m, 36 H), 1.76 (m, 2 H), 2.15 (s, 3 H), 2.51 (m, 8 H), 2.75 (t, *J* = 6.8 Hz, 2 H), 3.56 [s, 2 H, NCH_2C(5)], 3.63 [s, 2 H, NCH_2C(7)], 3.75 (m, 8 H), 10.6 (s, 1 H) ppm; NCH_2C(5) and NCH_2C(7) were assigned on the basis of NOE investigations involving the irradiation of CH_3C(8). EI-MS: *m*/*z* (%) = 600.5 (10) $[M]^+$, 513 (98) $[M - C_4H_8O]^+$, 426 (100) $[M - 2\ C_4H_8O]^+$, 203 (29), 165 (65) $[C_{10}H_{13}O_2]^+$, 43 (33). $C_{37}H_{64}N_2O_4$ (600.93): calcd. C 73.95, H 10.74, N 4.66; found C 74.0, H 10.84, N 4.65. The crude residue can be purified by column chromatography (hexane/AcOEt, 4:1 → AcOEt). Alternatively, **8a** can be converted into the corresponding hydrochloride as described for the synthesis of **6a**·HCl. From the TBME solution the crystalline dihydrochloride **8a**·2HCl was obtained as a colourless precipitate. The solid was filtered off and washed with TBME. Tocopherol salt **8a**·2HCl (1 g) was recrystallized from EtOH/Et_2O (15 mL) as colourless crystals. M.p. 144–147 °C. IR (KBr): $\tilde{\nu}$ = 3235 (w), 2951 (vs, sh), 2924 (vs), 2698 (m), 2675 (m), 2619 (m), 1256 (m), 1600 (m), 1498 (m), 1461 (vs), 1442 (vs, sh), 1428 (s, sh), 1405 (m), 1377 (s), 1354 (m), 1331 (m), 1268 (s), 1238 (m), 1203 (m), 1141 (s), 1125 (s), 1078 (s), 1071 (m), 1057 (m), 1020 (m), 1000 (m), 950 (m), 898 (m), 875 (m) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.85–1.58 (m, 36 H), 1.86 (t, *J* = 6.5 Hz, 2 H), 2.21 (s, 3 H), 2.82–3.30 (m, 6 H), 3.48 (m, 4 H), 3.95 (m, 4 H), 4.14–4.50 (m, 8 H), 9.28 (s, 1 H), 11.30 (s, 1 H), 11.46 (s, 1 H) ppm. ISP-MS: *m*/*z* (%) = 601.5 (100) $[M + H - 2\ HCl]^+$. $C_{37}H_{66}Cl_2N_2O_4$ (673.85): calcd. C 65.95, H 9.87, Cl 10.52, N 4.16; found C 65.84, H 9.77, Cl 10.42, N 4.11. Addition of 5% aq. NaOH to **8a**·2HCl followed by extraction with TMBE provided **8a** quantitatively.

(2*R*,4′*R*,8′*R*)-5-(Morpholinomethyl)-δ-tocopherol (9): The Mannich reagent derived from morpholine (2.8 g, 24 mmol, 1.2 equiv.) was added to mechanically stirred **4** (8.2 g, 20 mmol) at room temp. During addition of the morpholine reagent, the yellowish mixture became tarnished. Then the mixture was heated to 80 °C within about 15 min. After 1.5 h, the aminomethylation was almost complete (control by GLC, silylated derivative). Workup as described for **6a** afforded **9** (10.3 g) as a yellowish oil, 90.0% (GLC, silylated derivative). IR (film): $\tilde{\nu}$ = 2952 (vs, sh), 2926 (vs), 2853 (s, sh), 1468 (vs), 1378 (s), 1302 (m), 1223 (s), 1158 (m), 1120 (vs), 991 (m), 913 (m) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.70–1.64 (m, 36 H), 1.76 (m, 2 H), 2.11 (s, 3 H), 2.57–2.61 (6 H), 3.64 (s, 2 H), 3.74 (m, 4 H), 6.53 (s, 1 H), 10.4 (s, 1 H) ppm. EI-MS: *m*/*z* (%) = 501 (42) $[M]^{+\cdot}$, 414 (100) $[M - C_4H_8O]^+$, 189 (24), 43 (13). $C_{32}H_{55}NO_3$ (501.80): calcd. C 76.60, H 11.05, N 2.79; found C 76.40, H 11.09, N 2.94. This raw product was dissolved in TBME (400 mL) and gaseous HCl (30 mmol) was passed through the solution. A colourless precipitate was obtained. Removal of the solvent in vacuo and recrystallization of the solid residue from warm acetone (120 mL) afforded **9**·HCl (8.9 g, 83% yield) as colourless crystals in the form of druses. M.p. 152–154 °C. IR (KBr): $\tilde{\nu}$ = 3112 (s), 2951 (vs, sh), 2924 (vs), 2856 (s, sh), 2600 (m), 2555 (m, sh), 1460 (vs), 1423 (m), 1377 (s), 1366 (m, sh), 1237 (m), 1226 (s), 1125 (vs), 1104 (m), 918 (m) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.84–1.65 (m, 36 H), 1.79 (t, *J* = 6.5 Hz, 2 H), 2.09 (s, 3 H), 2.78 (t, *J* = 6.5 Hz, 2 H), 3.09 (m, 2 H), 3.40 (d, *J* = 12.0 Hz, 2 H), 3.89 (d, *J* = 12.0 Hz, 2 H), 4.22 (m, 4 H), 6.90 (s, 1 H), 8.04 (s, 1 H), 11.49 (s, 1 H) ppm. ISP-MS: *m*/*z* (%) = 515.5 (100) $[M - HCl]^+$. $C_{32}H_{56}ClNO_3$ (538.26): calcd. C 71.41, H 10.49, Cl 6.59, N 2.60; found C 71.45, H 10.45, Cl 6.63, N 2.80. The mother liquor of the above crystallization was treated with aq. NaOH and extracted with TBME as described below. Concentration under reduced pressure afforded a yellow oil containing 1.81% **4**, 42.92% **9**, 33.58% **10** and 13.24% **8a**. Compound **10** was identified by ^{1}H NMR spectroscopy (400 MHz, $CDCl_3$, only characteristic and identified signals): δ = 1.23 (s, 3 H), 2.10 (s, 3 H), 3.70 (s, 2 H), 6.41 (s, 1 H) ppm. Assignment of the signals was possible because of the known content of the mother liquor and by comparison with the ^{1}H NMR data of **9**. Tocopherol salt **9**·HCl (8.9 g, 16.6 mmol) was dissolved in TBME (100 mL) and 5% aq. NaOH (50 mL) was added. The resulting suspension was extracted five times with 50 mL of TBME each and the collected organic layers were dried (K_2CO_3). Concentration to dryness afforded **9** (8.3 g, 100% yield) as a slightly yellow oil.

Catalytic Hydrogenation of Aminomethylated Tocopherol Homologues:[7] The aminomethylated products (**6**–**10**) were hydrogenated in a 380-mL steel autoclave at 180 °C and 28–34 bar for 6–24 h using 5% palladium on carbon as the catalyst in TBME (5 wt.-%

in the normal case). After the hydrogenation, the catalyst was filtered off through Speedex (filter aid), rinsed with TBME and the solvent removed under reduced pressure. The liquid residue was distilled bulb-to-bulb in vacuo (180–200 °C/0.03 mbar).

Reduction of 7a to 1 Using $NaCNBH_3$: Compound **7a** (516 mg, 1 mmol) was dissolved in *i*BuOH (4 mL) and $NaBH_3CN$ (283 mg, 4.5 mmol, 4.5 equiv.) was added. The colourless suspension was refluxed (108 °C) and stirred for a further 4 h. Afterwards, the mixture was cooled to room temp., diluted with Et_2O (10 mL) and acidified to pH = 1 by addition of 2 N HCl (12 mL). The aqueous layer was separated and washed with Et_2O (2 × 5 mL). The organic layers were washed with satd. aq. $NaHCO_3$ (10 mL), satd. aq. NaCl (10 mL) and dried ($MgSO_4$). Concentration under reduced pressure to dryness afforded raw **1** (412 mg, 95.9% pure, GC, acetylated derivative). Further purification of 335 mg of raw **1** by column chromatography (20 g SiO_2, hexane/AcOEt, 9:1) gave pure **1** (332 mg, 89.6% yield) as a yellowish oil. Purity approx. 100% (GC, acetylated derivative). ^1H and ^{13}C NMR data are in accordance with reported data.[19]

Reduction of 7a to 1 Using $NaBH_4$/NaOH: Compound **7a** (516 mg, 1 mmol) was dissolved in *i*BuOH (20 mL) and $NaBH_4$ (160 mg, 4 mmol, 4 equiv.) and then NaOH (80 mg, 2 mmol, 2 equiv.) was added. The light yellow suspension was dipped in an oil bath at 120 °C and refluxed and stirred for 7 h. Afterwards, the mixture was cooled to room temp., further $NaBH_4$ was added (1 equiv.) and the mixture dipped again in the heated oil bath (120 °C) and refluxed for an additional 2 h. Afterwards, the mixture was cooled to room temp., diluted with Et_2O (10 mL) and acidified to pH = 4 by addition of 2 N HCl (ca. 11 mL). The aqueous layer was separated and washed with Et_2O (2 × 10 mL). The organic layers were washed with satd. aq. $NaHCO_3$ (10 mL), satd. aq. NaCl (10 mL) and dried ($MgSO_4$). After concentration under reduced pressure, the residue (raw **1**, purity >99%, HPLC) was purified by column chromatography (20 g SiO_2, hexane/AcOEt, 8:1), affording **1** (408 mg, 95% yield) as a yellowish oil. Purity approx. 100% (GC, acetylated derivative). ^1H and ^{13}C NMR data are in accordance with reported data.[19]

Characterization of *n*-Butyl α-Tocopheryl Ether (11): The *n*-butyl ether **11** was purified by column chromatography (hexane/AcOEt, 9:1) of the crude residue resulting from Bu_4NBH_4 reduction of **7a** carried out as described above for the reduction of **7a** to **1** by $NaCNBH_3$. Characteristic ^1H NMR signals in comparison with the ^1H NMR spectrum of α-tocopherol: absence of signal of OH; δ = 3.63 (t, J = 6.9 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.3, 11.8, 12.2, 14.0, 19.4, 19.6, 19.7, 20.7, 21.0, 22.6, 22.7, 23.8, 24.6, 24.9, 28.1, 31.4, 32.5, 32.7, 32.8, 37.3, 37.5, 37.6, 37.7, 39.4, 39.8, 72.8, 74.7, 117.4, 122.7, 125.8, 127.8, 147.6, 148.4 ppm. ISP-MS: m/z (%) = 487.8 (100) $[M + H]^+$.

β-Tocopherol (2) by $NaBH_4$/NaOH Reduction of 9: Reduction of **9** (500 mg, 1 mmol) using $NaBH_4$/NaOH as described above for the reduction of **7a** to **1** afforded **2** (380 mg, 95% yield). ^1H and ^{13}C NMR data are in accordance with reported data.[19]

(2*R*,4′*R*,8′*R*)-5-(Morpholino-[$^2H_2$]methyl)-γ-tocopherol (12): Preparation from **3** (4.21 g, 10 mmol) and the dideuteriated Mannich reagent derived from morpholine (4.77 g) and paradeuterioformaldehyde as described above for **7a** afforded **12** (5.14 g, 98.3% yield) as colourless crystals. M.p. 39–41 °C. Purity: 97.4% (GLC, silylated derivative). ^1H NMR (250 MHz, $CDCl_3$): δ = 0.83–1.65 (m, 36 H), 1.78 (m, 2 H), 2.10 (s, 3 H), 2.14 (s, 3 H), 2.60 (m, 6 H), 3.76 (m, 4 H), 10.57 (s, 1 H) ppm. ISP-MS: m/z (%) = 518.4 (100) $[M + H]^+$; deuterium content >99%. $C_{33}H_{55}D_2NO_3$ (517.84): calcd. C 76.54, H 11.48, N 2.70; found C 76.68, H 11.47, N 2.70.

(2*R*,4′*R*,8′*R*)-[C^5-^2H]-α-Tocopherol (13): Reduction of **7a** (1.03 g, 2 mmol) by $NaBD_4$/NaOH as described above for the transformation of **7a** to **1** afforded **13** (810 mg, 94% yield) as a yellowish oil. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.7–1.9 (m, 38 H), 2.11 (br. s, 5 H), 2.16 (s, 3 H), 2.61 (t, J = 7 Hz, 2 H), 4.17 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.3 (m), 11.8, 12.2, 19.9, 21.0, 21.2, 22.6, 22.7, 23.8, 24.6, 24.9, 28.1, 31.5, 32.7, 32.8, 37.3, 37.5, 37.6, 37.7, 39.4, 39.8, 74.6, 117.3, 118.7, 121.1, 122.6, 144.4, 145.6 ppm. ISP-MS: m/z (%) = 432.7 (100) $[M + H]^+$; deuterium content >99%. $C_{29}H_{49}DO_2$ (431.71): calcd. C 80.68, H 11.91; found C 80.65, H 11.94.

(2*R*,4′*R*,8′*R*)-[C^5-$^2H_2$]-α-Tocopherol (14): Reduction of **12** (777 mg, 1.5 mmol) using $NaBH_4$/NaOH as described above for the transformation of **7a** to **1** afforded **14** (610 mg, 94% yield) as a dark yellowish oil. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.7–1.9 (m, 38 H), 2.09 (s, 1 H), 2.11 (s, 3 H), 2.16 (s, 3 H), 2.58 (t, J = 7 Hz, 2 H), 4.16 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.3 (m), 11.8, 12.2, 19.9, 21.0, 21.2, 22.6, 22.7, 23.8, 24.6, 24.9, 28.1, 31.5, 32.7, 32.8, 37.3, 37.5, 37.6, 37.7, 39.4, 39.8, 74.6, 117.3, 118.7, 121.1, 122.6, 144.4, 145.6 ppm. ISP-MS: m/z (%) = 433.7 (100) $[M + H]^+$; deuterium content 98%. $C_{29}H_{48}D_2O_2$ (432.72): calcd. C 80.49, H 12.11; found C 80.46, H 12.09.

(2*R*,4′*R*,8′*R*)-[C^5-$^2H_3$]-α-Tocopherol (15): Reduction of **12** (800 mg, 1.54 mmol) using $NaBD_4$/NaOH as described above for the transformation of **7a** to **1** afforded **15** (610 mg, 95% yield) as a yellow oil. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.7–1.9 (m, 38 H), 2.11 (s, 3 H), 2.18 (s, 3 H), 2.60 (t, J = 7 Hz, 2 H), 4.19 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.3 (m), 11.8, 12.2, 19.9, 21.0, 21.2, 22.6, 22.7, 23.8, 24.6, 24.9, 28.1, 31.5, 32.7, 32.8, 37.3, 37.5, 37.6, 37.7, 39.4, 39.8, 74.6, 117.3, 118.7, 121.1, 122.6, 144.4, 145.6 ppm. ISP-MS: m/z (%) = 434.7 (100) $[M + H]^+$; deuterium content 98.5%. $C_{29}H_{47}D_3O_2$ (433.72): calcd. C 80.31, H 12.32; found C 80.34, H 12.34.

(2*R*,4′*R*,8′*R*)-5-(Morpholino-[$^2H_2$]methyl)-δ-tocopherol (16): Mannich reagent (510 mg, 2.8 mmol, 1.3 equiv.) was added to δ-tocopherol (870 mg, 2.16 mmol) and the resulting mixture was stirred at 80 °C for 2 h, TLC (hexane/EtOAc, 9:1) control confirming the end of the reaction. After cooling to room temp., the mixture was diluted with TBME (15 mL) and washed with H_2O until the wash solution became neutral. The organic layer was dried with K_2CO_3. Concentration to dryness gave **16** (860 mg, 80% yield) as a yellow oil. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.7–1.9 (m, 38 H), 2.11 (s, 3 H), 2.54–2.61 (m, 6 H), 3.74 (m, 4 H), 6.50 (s, 1 H), 10.39 (br. s, 1 H) ppm. ISP-MS: m/z (%) = 504.8 (100) $[M + H]^+$; deuterium content 98.5%. $C_{32}H_{53}D_2NO_3$ (503.80): calcd. C 76.29, H 11.40, N 2.78; found C 76.25, H 11.41, N 2.77.

(2*R*,4′*R*,8′*R*)-[C^5-$^2H_3$)-β-Tocopherol (17): Reduction of **16** (800 mg, 1.59 mmol) using $NaBD_4$/NaOH as described above for the transformation of **7a** to **1** afforded **17** (600 mg, 90% yield) as a yellow oil. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.7–1.9 (m, 38 H), 2.11 (s, 3 H), 2.59 (t, J = 7 Hz, 2 H), 4.25 (br. s, 1 H), 6.50 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.1 (m), 15.8, 19.6, 19.8, 21.0, 21.1, 22.7, 22.8, 23.8, 24.5, 24.9, 28.0, 31.3, 32.7, 32.8, 37.3, 37.5, 37.6, 37.7, 39.4, 39.6, 74.5, 115.3, 119.1, 120.3, 124.1, 145.7, 146.0 ppm. ISP-MS: m/z (%) = 420.8 (100) $[M + H]^+$; deuterium content 98.5%. $C_{28}H_{45}D_3O_2$ (419.70): calcd. C 80.13, H 12.25; found C 80.19, H 12.23.

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[1] a) W. A. Skinner, R. M. Parkhurst, J. Scholler, *J. Med. Chem.* **1969**, *12*, 64–66; b) H. J. Kayden, M. G. Traber, *J. Lipid Res.* **1993**, *34*, 343–358; c) R. Brigelius-Flohe, M. G. Traber, *FASEB J.* **1999**, *13*, 1145–1155.

[2] a) K. U. Baldenius, L. von dem Bussche-Hünnefeld, E. Hilgemann, P. Hoppe, R. Stürmer in *Ullmann's Encyclopedia of Industrial Chemistry*, VCH, Weinheim, **1996**, vol. A27, pp. 478–488, 594–597; b) T. Netscher, *Chimia* **1996**, *50*, 563–567.

[3] a) L. Weisler (Distillation Products Inc., Rochester, NY), U.S. Pat. 2486539, **1949**; *Chem. Abstr.* **1950**, *44*, 10278; b) L. Weisler (Eastman Kodak, Rochester, NY), U.S. Pat 2519863, **1950**; *Chem. Abstr.* **1951**, *45*, 3760.

[4] a) T. Nakamura, S. Kijima, *Chem. Pharm. Bull.* **1971**, *19*, 2318–2324; b) W. S. Baldwin, S. M. Willging, M. B. Siegel (Henkel Corporation), Eur. Pat. Appl. 0159018, priority **1984** (U.S. Pat. 601194); *Chem. Abstr.* **1986**, *104*, 95446; c) J. G. Baxter (Eastman Kodak, Rochester, NY), U.S. Pat. 2592531, **1952**; *Chem. Abstr.* **1953**, *47*, 4875.

[5] a) L. Weisler (Eastman Kodak, Rochester, NY), U.S. Pat. 2640058, **1951**; *Chem. Abstr.* **1954**, *48*, 42536.

[6] a) K. Brüggemann, J. R. Herguijuela, T. Netscher, J. Riegl (Hoffmann–La Roche AG), Eur. Pat. Appl. 0769497A1, **1997**, priority **1995** (CH 2951/95); *Chem. Abstr.* **1997**, *126*, 317507; b) J. Riegl, K. Brüggemann, T. Netscher in *Proc. ECSOC-3 (1999)*, *Proc. ECSOC-4 (2000)* (Ed.: E. Pombo-Villar), MDPI, Basel, Switzerland, **2000**, pp. 1542–1547; http://www.mdpi.org/ecsoc-4.htm; http://pages.unibas.ch/mdpi/ecsoc-4/c0035/c0035.htm.

[7] a) T. Netscher, R. K. Müller, J. Schneider, H. Schneider, P. Bohrer, R. Jestin in *12th European Symposium on Organic Chemistry*, Groningen, 13–18th July **2001**, poster; b) T. Netscher, R. K. Müller, J. Schneider, H. Schneider, P. Bohrer, R. Jestin in *Fifth International Electronic Conference on Synthetic Organic Chemistry (ECSOC-5)*, "Molecular Diversity Preservation International", Basel, Switzerland, **2001**; http://www.mdpi.net/ecsoc/ecsoc-5/Papers/c0007/c0007; c) R. K. Müller, H. Schneider (F. Hoffmann–La Roche AG), Eur. Pat. Appl. 0735033B1, **1996**, priority **1995** (CH 87895); *Chem. Abstr.* **1996**, *125*, 301271.

[8] a) F. Gu, T. Netscher, J. Atkinson, *J. Labelled Cpd. Radiopharm.* **2006**, *49*, 733–743; b) E. Alpi, F. Mazzini, T. Netscher, P. Salvadori, *4th Italian-Spanish Symposium on Organic Chemistry (ISSOC-4)*, 31st August to 3rd September, **2002** Perugia, Italy, contribution PO-44.

[9] S. Narasimhan, R. Balakumar, *Aldrichim. Acta* **1998**, *31*, 19–26, and references cited herein.

[10] H. C. Brown, S. Narasimhan, Y. M. Choi, *J. Org. Chem.* **1982**, *47*, 4702–4708.

[11] H. C. Brown, S. Krishnamurthy, *Tetrahedron* **1979**, *35*, 567–607.

[12] J. R. Berschied, K. F. Purcell, *Inorg. Chem.* **1970**, *9*, 624–629.

[13] E. H. Jensen, *A Study on Sodium Borohydride*, NytNordisk Forlag Amold Busck, Copenhagen, **1954**.

[14] T. Rosenau, G. Ebner, A. Stanger, S. Perl, L. Nuri, *Chem. Eur. J.* **2005**, *11*, 280–287, and references cited herein.

[15] T. Rosenau, L. Gille, E. Kloser, F. Mazzini, T. Netscher, unpublished results.

[16] a) K. U. Ingold, L. Hughes, M. Slaby, G. W. Burton, *J. Labelled Cpd. Radiopharm.* **1987**, *24*, 817–831; b) L. Hughes, M. Slaby, G. W. Burton, K. U. Ingold, *J. Labelled Cpd. Radiopharm.* **1990**, *28*, 1049–1057.

[17] A. Brändström, U. Junggren, B. Lamm, *Tetrahedron Lett.* **1972**, *13*, 3173–3176.

[18] a) W. Walther, T. Netscher, *Chirality* **1996**, *8*, 397–401; b) N. Cohen, C. G. Scott, C. Neukom, R. J. Lopresti, G. Weber, G. Saucy, *Helv. Chim. Acta* **1981**, *64*, 1158–1173.

[19] J. K. Baker, C. W. Myers, *Pharmaceutical Res.* **1991**, *8*, 763–770.

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