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Efficient Synthesis of Vitamin E Amines

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A short and efficient synthesis of all VE amines (α-, β-, γ-, δ-tocopheramines and -tocotrienamines) in enantiopure form is described. These amino analogues of natural vitamin E compounds (α-, β-, γ-, δ-tocopherols and -tocotrienols) can be prepared by Pd-catalyzed *N*-arylation reactions on the corresponding triflates, synthesized under controlled conditions from the phenols. The benzophenone imine or benzylamine intermediates deliver the VE amines in high yield and purity after deprotection. The compounds prepared are key precursors of VE amides, which are of great interest in the search for new therapeutics with antitumoral activity.

Introduction

Vitamin E (VE) is a term that encompasses a group [four tocopherols and four tocotrienols (Figure 1)] of lipid-soluble, biologically essential compounds derived from 6-chromanol that exhibit the biological activity of α-tocopherol. In 1942, Smith et al. reported that the amino analogue of (*all-rac*)-α-tocopherol, (*all-rac*)-α-tocopheramine, had approximately the same properties as α-tocopherol itself.[1] Since that discovery, different racemic tocopheramines have been found to exhibit biological and antioxidant activities similar to the corresponding tocopherols and in some cases even higher activities.[2,3] As tocopheramines are nontoxic, these properties have made their use as food additives,[4] polymer stabilizers,[5] and precursors of surfactants and pharmaceutical excipients[6] effective and thus attractive. Moreover, VE amides derived from α- and δ-tocopheramines have recently[7] been shown to be potent anticancer agents, exhibiting higher proapoptotic activity than the structurally related ester α-tocopheryl succinate, the antitumoral activity of which has been well assessed in several studies.[8,9]

The syntheses of tocopheramines reported up to a few years ago were low-yielding multistep procedures. They were basically modifications of the classic route to tocopherols, involving the acid-catalyzed condensation of the appropriate formylamino- or aminophenol with phytol or isophytol.[10] One of the disadvantages of these routes is that no optical activity can be introduced into the chromane part, providing only epimeric mixtures of tocopheramines. Recently, Lambert and Lal[6] described the synthesis of the optically pure amine **1d** in four steps starting from the optically pure (2*R*,4′*R*,8′*R*)-α-tocopherol (**1a**; Figure 1). Phenol **1a** was converted into the tosylate or triflate ester and deoxygenated by Pd- or Ni-catalyzed hydrogenation or metal hydride reduction. Nitrogen was then introduced at C6 by a nitration reaction and finally another catalytic hydrogenation step afforded the optically pure α-tocopheramine. In particular, the chiral centers present in the starting material and their configurations were maintained through all the reactions. The possibility of preparing stereopure VE amines allows the study of the importance of their stereochemistry in the expression of their biological

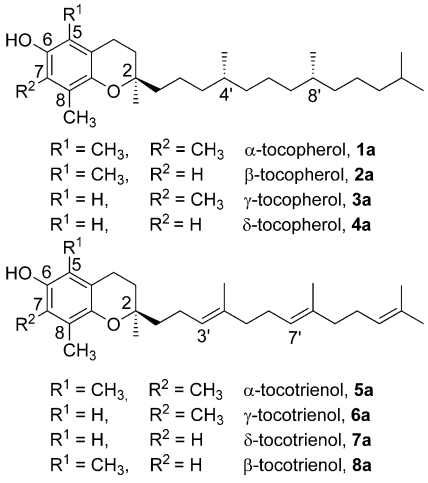

Figure 1. Structures of natural tocopherols and tocotrienols (VE compounds).

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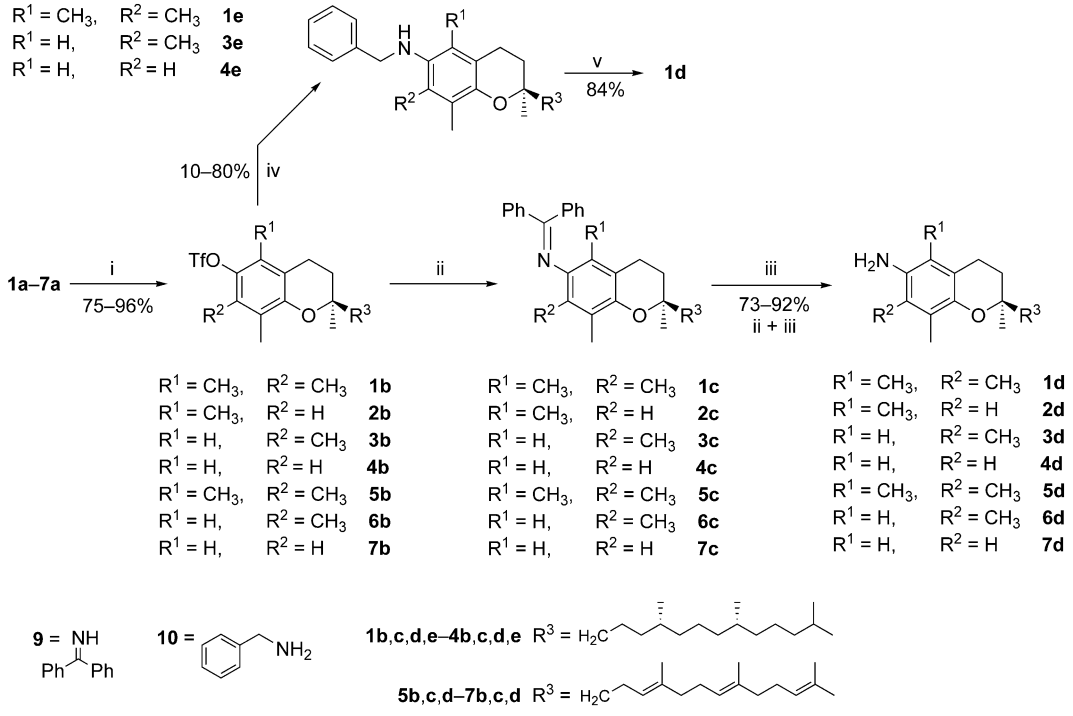

i. Tf_2O, CH_2Cl_2, 2,6-lutidine, –10 °C, 3 h. ii. $Pd(OAc)_2$, BINAP, **9**, NaO*t*Bu or Cs_2CO_3, toluene (80 °C) or dioxane (100 °C), 5 h. iii. THF/2 M HCl, 30 min to 2 h. iv. $Pd(OAc)_2$, BINAP, **10**, NaO*t*Bu, toluene, 80 °C, 16 h. v. Pd/C, MeOH, HCO_2NH_4, reflux, 1h.

Scheme 1. Preparation of VE amines **1d**–**7d**.

properties, for instance, in the transport protein recognition pathway, which has already been disclosed for tocopherols and tocotrienols.[11]

Very recently, following the approach outlined by Lambert and Lal,[6] **1d** was prepared in 48% yield in four steps starting from triflate **1b**.[12] In agreement with the data reported by these authors, in our trials deoxygenation of **1b** proceeded smoothly by Pd/C hydrogenation in the presence of Et_3N, whereas it proved resistant to the $NaBH_4$/$NiCl_2{\cdot}6H_2O$ and $[PdCl_2(PPh_3)_2]$/Dppp/Bu_3N reduction systems. However, the subsequent nitration step gave low-to-moderate yields and its application to the other VE homologues provided complex mixtures.[12]

On the basis of these results and the interest in VE amines, we decided to look for a simpler and more general procedure for the synthesis of **1d**–**7d** (Scheme 1) to make them more easily available. Therefore we turned our attention to Pd-catalyzed aryl amination. Buchwald[13] and Hartwig[14] have independently developed a strategy for the Pd-catalyzed amination of aryl halides or pseudo-halides that is a mild and widely applicable alternative to the classic methods of aryl C–N bond formation. Herein we report its efficient application to the preparation of VE amines **1d**–**7d**.

Results and Discussion

The synthesis of optically pure as well as racemic tocopheramines by Pd-mediated amination of α-, γ-, and δ-tocopheryl triflates has recently been performed by Netscher and co-workers.[15] A similar approach has also been followed by others in the successful preparation of **4d**.[12]

Therefore, we have optimized the strategy and extended it to the synthesis of tocotrienamines (Scheme 1). To introduce a nitrogen function at the 6-position of the chromane ring we investigated the use of the ammonia equivalent benzophenone imine (**9**)[16] and benzylamine (**10**),[17] which easily provide the free aniline by acidic hydrolysis (or transamination) and by mild hydrogenolysis with ammonium formate using Pd/C, respectively.

Classic procedures [anhydrous CH_2Cl_2, triflic anhydride (Tf_2O), base][15,18] were followed for the synthesis of triflates **1b**–**7b**, but unexpected results were obtained in the preparation of the tocotrienyl triflates. When mixing all the reactants at once, that is, tocotrienol, base (Et_3N/DMAP), and Tf_2O in CH_2Cl_2 at –10 °C, conversion was complete within 3 h, but the product isolated after column chromatography (*n*-hexane/EtOAc, 20:1) showed an NMR spectrum with some inconsistencies, although MS analysis delivered the expected results. In particular, signals in the olefinic proton region of the ^1H NMR spectrum gave unusually complex patterns and integral values that account for less than three protons. Moreover, in the ^{13}C NMR spectrum some signals were doubled, in particular the signal representing C2 of the chromane ring. Carrying out the reaction at –20 °C and using NaH as the base gave the same results. We supposed that some kind of rearrangement and/or the cyclization of the unsaturated terpenoic side-chain were catalyzed by Tf_2O

(or TfOH formed during the reaction), providing tocotrienyl triflate isomers. In one set of experiments, Tf_2O was added slowly dropwise to a CH_2Cl_2 solution of tocotrienol **6a** and excess 2,6-lutidine at –60, –30, and –10 °C. Triflate **6b**, showing the expected NMR spectrum, was obtained in 85% yield in each of the three trials, which suggests that the critical point of the reaction is the rate of Tf_2O addition rather than the temperature or type of base. The other VE triflates were obtained in yields of 75–96% (unoptimized) in 3 h at –20 to –10 °C (Scheme 1).

The first amination reaction was performed on **1b**. $Pd(OAc)_2$ (5 mol-%) and *rac*-BINAP (6.5 mol-%) were stirred in toluene for 30 min[19] at room temp. To this mixture, first a toluene solution of **1b** and amine **10** or imine **9** was added followed after a few minutes by NaO*t*Bu (1.3 equiv.). Complete conversion was obtained at 80 °C in 16 h with **10** and in 5 h with **9**. Amine **1e** was purified by column chromatography and isolated in a yield of 80% and then heated at reflux for 30 min in MeOH in the presence of $HCOONH_4$ (3 equiv.) and Pd/C (10%)[20] to give **1d** in an 84% isolated yield.

The benzophenone imine route was easier to perform from an experimental point of view and more efficient in terms of yields. Isolation of imine **1c** was carried out by chromatography of the crude mixture on a short column of silica gel, collecting only the eluate corresponding to the strong-yellow band. This band contained, besides **1c**, only a small amount of benzophenone, which results from the cleavage by silica gel of the slight excess of the benzophenone imine used in the reaction. As benzophenone was also formed in the following hydrolysis step, better purification was unnecessary at this stage. The collected fraction was treated with 2 M HCl in THF for 2 h at room temp. Alternatively, the rate of hydrolysis could be increased by gentle warming of the reaction mixture, completion being attained in 30 min at 50 °C. Benzophenone was thus easily separated from **1d** by column chromatography, affording the amine in 79% yield with respect to **1b**. No cleavage of the imine adducts **1c**–**7c** by silica gel to yield **1d**–**7d** was observed. Racemic α-tocopheramine was prepared by the same protocol starting from the commercially available (*all-rac*)-α-tocopherol. As sterically hindered *ortho*-substituted aryl halides[21] and nonaflates[22] have been reported to successfully undergo amination with **9** by using $[Pd_2dba_3]$, we also used the $[Pd_2dba_3]$ (3–5 mol-%) and BINAP catalytic system, but conversions were significantly lower than those achieved by $Pd(OAc)_2$-catalyzed amination.

The benzylamine route was then followed to prepare just the *N*-benzyl-γ- and -δ-tocopheramines **3e** and **4e** as their antioxidant and biological properties have never been investigated before. Compounds **3e** and **4e** were obtained in 67 and 10% yields, respectively. Several byproducts were formed in these reactions, likely due to over-arylation of the primary amine,[19] a side-reaction not shared by the benzophenone imine adducts.

In one of the experiments, traces of α-tocopherol were detected by TLC analysis, very likely arising from cleavage of the corresponding triflate by NaO*t*Bu.[22,23] The use of Cs_2CO_3 in place of NaO*t*Bu has been reported to provide similarly high efficiency while preventing triflate hydrolysis in amination reactions.[23] In fact, the formation of **1a** was not observed in the coupling reaction of **1b** with **9** or **10** in the presence of Cs_2CO_3, but the yields of **1c** and **1e** decreased dramatically in both toluene and 1,4-dioxane, not exceeding 37% after prolonged heating. The amination of **5b** in the presence of Cs_2CO_3 showed the same trend, and thus **5d** was obtained in 73% with respect to **5b** by using **9** and NaO*t*Bu as base.

In contrast, when Cs_2CO_3 was employed together with **9** in the synthesis of **2d**, **3d**, and **6d** (with 1,4-dioxane as solvent), complete conversion was observed after heating at reflux for 5 h. The acidic hydrolysis was faster than for the α series, that is, 30 min at room temp., probably because of the lower steric hindrance at C6, affording the desired VE amines **2d**, **3d**, and **6d** in 87, 83, and 82% yields with respect to the corresponding triflates. Compound **3d** was also obtained in a similar yield (88%) in 5 h by using NaO*t*Bu in toluene at 85 °C; the formation of **3a** was not observed.

Unexpectedly, the triflates of the δ VE series reacted more slowly than those of the β and γ series when Cs_2CO_3 was used as the base. The amination of **4b** under the same reaction conditions employed for the preparation of **3d** provided only 50% conversion of the starting triflate after heating at reflux for 5 h. Increasing the loading of $Pd(OAc)_2$ to 10 mol-% improved the conversion to 76% after heating at reflux for 5 h, with further increments in the catalyst loading changing the outcome of the reaction slightly. In our hands, changing the catalyst to $[Pd_2dba_3]$[12] afforded significantly worse results. Conversely, 82% conversion was obtained after 5 h by using 5 mol-% of $Pd(OAc)_2$ in toluene at 85 °C with NaO*t*Bu as the base, whereas complete conversion was achieved under the same conditions and reaction time but by starting with 7.5 mol-% of $Pd(OAc)_2$. Following the latter amination protocol and after acidic hydrolysis, **4d** and **7d** were synthesized in yields of 92% with respect to the starting triflates. The reasons for the different behaviour of the two series of homologues are not known. One possible explanation could be an inhibition of the catalytic system caused by the imine adduct of the δ series. Less steric hindrance than in the γ or β homologues could result in more effective competition with BINAP for palladium. In fact, in a set of experiments carried out using Cs_2CO_3, we observed a marked slow down of the amination rate of **4b** after 4–5 h. Further addition of only BINAP led to a greater conversion than obtained with the addition of $Pd(OAc)_2$.

Chiral HPLC analysis confirmed that the amines were obtained in enantiomerically pure form, as shown by comparison of their chromatograms with those of the corresponding racemic products, synthesized according to the same amination procedure.

Conclusions

An easy and efficient procedure for the synthesis of enantiopure tocopheramines and tocotrienamines has been

developed and optimized. VE amines were obtained in very good overall yields in three steps (63–88%) with retention of the configuration of the starting tocopherols/tocotrienols. In particular, the key reaction, *N*-aryl amination, was optimized to provide complete conversion of the corresponding tocopheryl/tocotrienyl triflates (prepared with Tf_2O and an excess 2,6-lutidine in CH_2Cl_2) in 5 h and the desired compounds in 73–92% yields after acidic hydrolysis, thus making optically pure VE amines easily available. The antioxidant and therapeutic properties of the compounds prepared in this way are currently under investigation. In a preliminary study, **1d** showed interesting antiproliferative effects (IC_{50} = 150 nm) on the neuroblastoma glioma C6 cancer cell line, that is, it is 100-fold more active than α-tocopherol in the same test.[24]

Experimental Section

General: All reactions were performed under an inert atmosphere (Ar or N_2). NMR spectra were obtained at 300 (^{1}H) and 75 MHz (^{13}C) using $CDCl_3$ as internal standard. Chemical shifts are expressed on the δ scale (ppm). Toluene was dried with Na, and 1,4-dioxane and CH_2Cl_2 with CaH_2 before use. All other commercial reagents were used without further purification. Column chromatography was performed on silica gel 60 (70–230 and 230–400 mesh). TLC was performed on silica gel (Macherey–Nagel Alugram Sil G/UV_{254}, 0.20 mm). UV spectra were measured with a Perkin-Elmer Lambda 650 spectrophotometer. MS (APCI) spectra were recorded using CH_3CN sample solutions. All yields given refer to isolated yields. Conversions were determined by HPLC on a LUNA Silica(2) column (250 × 4.6 mm, 5 μm, from Phenomenex); eluent: *n*-hexane/THF (100:1), flow: 1 mL/min, λ = 220 nm. (*R*,*R*,*R*)-α-Tocopherol (**1a**) was obtained from Henkel (from natural sources, Covitol F1490). (all-*rac*)-γ-Tocopherol and *rac*-α-tocotrienol were synthesized at DSM Nutritional Products (former Roche Vitamins and F. Hoffmann-La Roche). Tocopherols **2a**–**4a** were obtained by flash chromatographic purification (*n*-hexane/AcOEt, 88:12) of tocopherol concentrate, "d-Mixed Tocopherols" from Bizen Chemical Co., Ltd. (Okayama, Japan), as described by us in a previous paper.[25] Tocotrienols **5a**–**7a** were obtained by flash chromatographic purification (*n*-hexane/Et_2O, 10:1 to 2:1) of "Natural tocopherol-free tocotrienol concentrate (min. 97%)" from Davos Life Sciences. The stereopurity was determined by HPLC on a Chiralcel OD-H column (eluent: 0.5% EtOH in *n*-hexane, flow: 1.0 mL/min, λ = 220 nm). Racemic α-tocotrienamine, and α- and γ-tocopheramine were prepared according to the procedures described for the preparation of **5d**, **1d**, and **3d**, respectively. According to our experience of VE chemistry, the procedures used for VE amine synthesis are not expected to alter the configuration of the chiral centers in the starting tocopherols/tocotrienols, in particular, the chiral centers in the aliphatic side-chains. Thus, the configurations were assigned on the basis of the latter considerations, the order of elution of the VE compounds on the OD-H column under the same conditions,[26] and a comparison of the HPLC chromatograms of the amines of racemic and enantiopure tocopherols/tocotrienols.

General Procedure for VE Triflate Synthesis: The general procedure described below was used for the synthesis of all triflates, including for racemic ones. The characterization data and yields of the latter were the same as the optically pure triflates. In a general procedure, a solution of Tf_2O (1.46 g, 0.87 mL, 5.2 mmol, 1.3 equiv.) in dry CH_2Cl_2 (10 mL) was slowly added over 1 h to a solution of phenol **1a**–**7a** (4 mmol) and 2,6-lutidine (1.29 g, 1.4 mL, 12 mmol, 3 equiv.) in dry CH_2Cl_2 (10 mL) at –20 to –10 °C. The mixture was stirred at –10 °C for a further 2 h and warmed to room temp. Complete conversion was confirmed by TLC (*n*-hexane/EtOAc, 10:1). A 5% $NaHCO_3$ solution was added to the deep-red solution and the aqueous phase extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phase was washed with 1 M HCl, 5% $NaHCO_3$, and brine, and then dried with anhydrous Na_2SO_4. After the removal of the solvent under vacuum, the crude red mixture was purified by column chromatography (*n*-hexane/EtOAc, 10:1).

(2*R*,4′*R*,8′*R*)-α-Tocopheryl Trifluoromethanesulfonate (1b): Yield 1.96 g (87%), pale-yellow oil. ^{1}H NMR[27] (300 MHz, $CDCl_3$): δ = 0.84–1.61 (m, 36 H), 1.72–1.88 (m, 2 H), 2.10 (s, 3 H), 2.19 (s, 3 H), 2.23 (s, 3 H), 2.61 (t, *J* = 6.9 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.0, 13.2, 14.0, 19.7, 19.8, 20.7, 21.0, 22.6, 22.7, 23.9, 24.5, 24.8, 28.0, 30.9, 32.7, 32.8, 37.3, 37.4, 37.5, 39.4, 40.0, 75.6, 118.4, 118.6 (q, J_{CF} = 318 Hz), 124.3, 126.6, 128.0, 139.6, 150.8 ppm. MS (APCI): *m*/*z* = 563.9 [M + H]$^+$. $C_{30}H_{49}F_3O_4S$ (562.77): calcd. C 64.03, H 8.78, S 5.70, F 10.13; found C 63.95, H 8.79, S 5.72, F 10.15.

(2*R*,4′*R*,8′*R*)-β-Tocopheryl Trifluoromethanesulfonate (2b): Yield 2.06 g (94%), pale-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84–1.65 (m, 36 H), 1.85–1.92 (m, 2 H), 2.19 (s, 3 H), 2.24 (s, 3 H), 2.62 (t, *J* = 6.9 Hz, 2 H), 6.92 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.4, 16.1, 19.7, 19.8, 20.8, 21.0, 22.7, 22.8, 23.9, 24.6, 24.9, 28.1, 30.8, 32.8, 32.9, 37.4, 37.5, 37.6, 39.5, 40.0, 75.8, 118.9 (q, J_{CF} = 320 Hz), 120.6, 121.0 125.6, 126.8, 140.6, 151.5 ppm. MS (APCI): *m*/*z* = 549.8 [M + H]$^+$. $C_{29}H_{47}F_3O_4S$ (548.74): calcd. C 63.47, H 8.63, S 5.84, F 10.39; found C 63.55, H 8.62, S 5.81, F 10.32.

(2*R*,4′*R*,8′*R*)-γ-Tocopheryl Trifluoromethanesulfonate (3b): Yield 1.80 g (82%), pale milky oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85–1.65 (m, 36 H), 1.71–1.82 (m, 2 H), 2.13 (s, 3 H), 2.22 (s, 3 H), 2.73 (t, *J* = 6.6 Hz, 2 H), 6.81 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.1, 13.1, 19.6, 19.7, 20.9, 21.0, 22.2, 22.6, 22.7, 24.1, 24.4, 24.8, 28.0, 30.7, 32.6, 32.8, 37.3, 37.4, 37.5, 39.4, 40.2, 76.3, 118.7 (q, J_{CF} = 319 Hz), 118.5, 119.1, 127.0, 127.8, 141.0, 151.2 ppm. MS (APCI): *m*/*z* = 549.8 [M + H]$^+$. $C_{29}H_{47}F_3O_4S$ (548.74): calcd. C 63.47, H 8.63, S 5.84, F 10.39; found C 63.70, H 8.59, S 5.79, F 10.35.

(2*R*,4′*R*,8′*R*)-δ-Tocopheryl Trifluoromethanesulfonate (4b): Yield 2.05 g (96%), pale-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83–1.62 (m, 36 H), 1.69–1.85 (m, 2 H), 2.18 (s, 3 H), 2.76 (t, *J* = 6.3 Hz, 2 H), 6.81 (d, *J* = 3 Hz, 1 H), 6.85 (d, *J* = 3 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.1, 19.6, 19.7, 20.9, 22.4, 22.6, 22.7, 24.1, 24.4, 24.8, 28.0, 30.7, 32.7, 32.8, 37.3, 37.4, 37.5, 39.4, 40.2, 76.6, 118.8 (q, J_{CF} = 315 Hz), 119.0, 120.7, 121.7, 128.3, 141.5, 151.7 ppm. MS (APCI): *m*/*z* = 535.8 [M + H]$^+$. $C_{28}H_{45}F_3O_4S$ (534.71): calcd. C 62.89, H 8.48, S 6.00, F 10.66; found C 62.75, H 8.50, S 6.05, F 10.65.

(2*R*,3′*E*,7′*E*)-α-Tocotrienyl Trifluoromethanesulfonate (5b): Yield 1.94 g (87%), pale-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (s, 3 H), 1.63–1.85 (m, 16 H), 1.94–2.15 (m, 13 H), 2.20 (s, 3 H), 2.23 (s, 3 H), 2.61 (t, *J* = 6.6 Hz, 2 H), 5.12 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.1, 13.1, 15.9, 16.0, 17.6, 22.1, 22.2, 24.1, 25.7, 26.6, 26.8, 30.8, 39.7, 39.8, 39.9, 75.4, 118.4, 118.7 (q, J_{CF} = 315 Hz), 124.1, 124.2, 124.4, 126.7, 128.1, 131.2, 135.0, 135.3, 139.7, 150.8 ppm. MS (APCI): *m*/*z* = 557.8 [M + H]$^+$. $C_{30}H_{43}F_3O_4S$ (556.72): calcd. C 64.72, H 7.79, S 5.76, F 10.24; found C 64.69, H 7.74, S 5.85, F 10.29.

(2*R*,3′*E*,7′*E*)-γ-Tocotrienyl Trifluoromethanesulfonate (6b): Yield 1.84 g (85%), pale milky oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31 (s, 3 H), 1.60–1.90 (m, 16 H), 1.94–2.20 (m, 13 H), 2.24 (s, 3 H), 2.77 (t, J = 6.6 Hz, 2 H), 5.11 (m, 3 H), 6.82 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.1, 13.1, 15.9, 16.0, 17.6, 22.1, 22.2, 24.1, 25.7, 26.6, 26.8, 30.8, 39.7, 39.8, 39.9, 76.5, 118.7 (q, J_{CF} = 315 Hz), 118.6, 119.1, 124.0, 124.1, 124.4, 127.0, 127.8, 131.2, 135.0, 135.4, 141.1, 151.1 ppm. MS (APCI): m/z = 543.9 $[M+H]^+$. $C_{29}H_{41}F_3O_4S$ (542.69): calcd. C 64.18, H 7.61, S 5.91, F 10.50; found C 64.15, H 7.64, S 5.99, F 10.55.

(2*R*,3′*E*,7′*E*)-δ-Tocotrienyl Trifluoromethanesulfonate (7b): Yield 1.59 g (75%), pale-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (s, 3 H), 1.57–1.90 (m, 16 H), 1.94–2.19 (m, 13 H), 2.78 (t, J = 6.6 Hz, 2 H), 5.11 (m, 3 H), 6.81 (d, J = 2.7 Hz, 1 H), 6.86 (d, J = 2.7 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.9, 16.0, 16.1, 17.6, 22.1, 22.4, 24.1, 25.7, 26.6, 26.8, 30.7, 39.7, 39.8, 39.9, 76.6, 118.8 (q, J_{CF} = 315 Hz), 119.0, 120.7, 121.7, 123.9, 124.1, 124.4, 128.4, 131.2, 135.0, 135.4, 141.5, 151.6 ppm. MS (APCI): m/z = 529.7 $[M+H]^+$. $C_{28}H_{39}F_3O_4S$ (528.67): calcd. C 63.61, H 7.44, S 6.07, F 10.78; found C 63.72, H 7.51, S 6.10, F 10.71.

General Procedure for Pd-Catalyzed Amination Using Benzylamine: In a typical procedure, $Pd(OAc)_2$ (12 mg, 0.05 mmol) and *rac*-BINAP (41 mg, 0.065 mmol) in dry toluene (3 mL) were stirred for about 30 min at room temp. Then, first a solution of **1b** (or **3b** or **4b**, 1 mmol) and **10** (217 mg, 0.2 mL, 1.2 mmol) in dry toluene (3 mL) was added to the catalyst mixture at room temp. followed after a few minutes by NaO*t*Bu (125 mg, 1.3 mmol). The resulting mixture was heated at 80 °C for 16 h. Complete conversion of the starting triflate was confirmed by HPLC analysis. The reaction mixture was cooled to room temp., diluted with diethyl ether (40 mL), and filtered through a plug of Celite. After removal of the solvent under vacuum, the crude mixture was purified by column chromatography (*n*-hexane/EtOAc, 95:5).

(2*R*,4′*R*,8′*R*)-*N*-Benzyl-α-tocopheramine (1e): Yield 416 mg (80%), amber oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84–0.88 (m, 12 H), 1.05–1.45 (m, 24 H), 1.75–1.83 (m, 2 H), 2.12 (s, 3 H), 2.18 (s, 3 H), 2.23 (s, 3 H), 2.40 (br. s, 1 H), 2.63 (t, J = 6.8 Hz, 2 H), 3.91 (s, 2 H), 7.24–7.44 (m, 5 H) ppm. $[\alpha]_D^{20}$ = +6.1 (c = 1.04, CH_2Cl_2). MS (APCI): m/z = 520.8 $[M+H]^+$. $C_{36}H_{57}NO$ (519.84): calcd. C 83.18, H 11.05, N 2.69; found C 83.13, H 10.99, N 2.75.

(2*R*,4′*R*,8′*R*)-*N*-Benzyl-γ-tocopheramine (3e): Yield 339 mg (67%), amber oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83–0.88 (m, 12 H), 1.04–1.60 (m, 24 H), 1.65–1.79 (m, 2 H), 2.06 (s, 3 H), 2.14 (s, 3 H), 2.66 (t, J = 6.4 Hz, 2 H), 3.00 (br. s, 1 H), 4.26 (s, 2 H), 6.26 (s, 1 H), 7.23–7.42 (m, 5 H) ppm. $[\alpha]_D^{20}$ = +17.3 (c = 1.06, CH_2Cl_2). MS (APCI): m/z = 506.6 $[M+H]^+$. $C_{35}H_{55}NO$ (505.82): calcd. C 83.11, H 10.96, N 2.77; found C 83.14, H 10.85, N 2.82.

(2*R*,4′*R*,8′*R*)-*N*-Benzyl-δ-tocopheramine (4e): Yield 50 mg (10%), amber oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83–0.90 (m, 12 H), 1.04–1.45 (m, 24 H), 1.67–1.79 (m, 2 H), 2.10 (s, 3 H), 2.66 (t, J = 6.7 Hz, 2 H), 3.05 (br. s, 1 H), 4.23 (s, 2 H), 6.21 (d, J = 2.6 Hz, 1 H), 6.36 (d, J = 2.6 Hz, 1 H), 7.30–7.38 (m, 5 H) ppm. $[\alpha]_D^{20}$ = +12.1 (c = 1.06, CH_2Cl_2). MS (APCI): m/z = 492.4 $[M+H]^+$. $C_{34}H_{53}NO$ (491.79): calcd. C 83.04, H 10.86, N 2.85; found C 83.19, H 10.80, N 2.89.

Preparation of 1d by the Hydrogenolysis of 1e: $HCOONH_4$ (190 mg, 3 mmol) was added to a suspension of **1e** (520 mg, 1 mmol) and 10% Pd/C (530 mg) in MeOH (10 mL), and the resulting black suspension was stirred at reflux for 1 h. After filtering through Celite and removal of the solvent under vacuum, the crude product was purified by column chromatography (*n*-hexane/EtOAc, 9:1) to afford **1d** (360 mg, 84% yield) as an amber oil.

General Procedure for Pd-Catalyzed Amination Using Benzophenone Imine: Dry toluene and dry 1,4-dioxane were used in the amination reactions carried out in the presence of NaO*t*Bu and Cs_2CO_3 as base, respectively. The reaction temperature was 85 °C using toluene and 100 °C using 1,4-dioxane. There were no other differences in the reaction protocol employing Cs_2CO_3 or NaO*t*Bu. Increasing the loading of Cs_2CO_3 from 1.6 to 3 equiv. did not provide a substantial improvement in yield. The representative amination procedure given below was used for the synthesis of all the imine adducts **1c**–**7c**, and also for the racemic ones. In a typical procedure, $Pd(OAc)_2$ (12 mg, 0.05 mmol) and *rac*-BINAP (41 mg, 0.065 mmol) in dry toluene (3 mL) were stirred under argon for about 30 min at room temp. Then, first a solution of **1b**–**7b** (1 mmol) and **9** (217 mg, 0.2 mL, 1.2 mmol) in dry toluene (3 mL) was added to the catalyst mixture at room temp. followed after a few minutes by NaO*t*Bu (125 mg, 1.3 mmol). The resulting mixture was heated at 80 °C for 5 h. Complete conversion of the starting triflate was confirmed by HPLC analysis. The reaction mixture was cooled to room temp., diluted with diethyl ether, (40 mL) and filtered through a plug of Celite. The crude product was concentrated and partially purified by chromatography through a short column (SiO_2, *n*-hexane/EtOAc, 7:1), collecting the eluate from the strong-yellow band. This fraction contained mainly the imine adducts **1c**–**7c** and only a small amount of benzophenone. After removal of the solvent under vacuum, an orange-yellow crude mixture was obtained ready for the subsequent hydrolysis step. Pure fractions of **1c**–**7c** were isolated by a more accurate column chromatographic purification procedure to allow their characterization (see the Supporting Information).

General Procedure for the Hydrolysis of 1c–7c: In a general procedure, a 2 M HCl solution (3 mL) was added to a solution in THF (5 mL) of the crude product isolated after the amination reaction of **1b**–**7b** with **9**. After 30 min at room temp. (for **1c** and **5c** 2 h at room temp. or 30 min at 50 °C) the orange solution turned to pale yellow and complete conversion was confirmed by TLC (*n*-hexane/EtOAc, 6:1). A 1 M NaOH solution (10 mL) was added and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with brine and dried with anhydrous Na_2SO_4. After removal of the solvent under vacuum, the crude yellow-orange mixture was purified by column chromatography (SiO_2, *n*-hexane/EtOAc, 5:1 to 2:1).

(2*R*,4′*R*,8′*R*)-α-Tocopheramine (1d): Yield 340 mg (79% with respect to **1b**), amber oil. UV (EtOH): ε (λ_{max}) = 3780 $dm^3\,mol^{-1}\,cm^{-1}$ (301 nm).[28] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81–1.68 (m, 36 H), 1.76–1.86 (m, 2 H), 2.08 (s, 3 H), 2.14 (s, 3 H), 2.17 (s, 3 H), 2.66 (t, J = 6.6 Hz, 2 H), 3.28 (br. s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.9, 12.6, 13.6, 19.7, 19.8, 21.1, 22.7, 22.8, 23.8, 24.5, 24.9, 28.0, 31.9, 32.8, 32.9, 37.4, 37.5, 37.6, 39.4, 39.9, 74.3, 117.1, 117.7, 120.4, 122.3, 134.9, 144.8 ppm. $[\alpha]_D^{23}$ = +3.7 (c = 1.0, EtOH). MS (APCI): m/z = 430.9 $[M+H]^+$. $C_{29}H_{51}NO$ (429.72): calcd. C 81.05, H 11.96, N 3.26; found C 81.24, H 11.94, N 3.21.

(2*R*,4′*R*,8′*R*)-β-Tocopheramine (2d): Yield 362 mg (87% with respect to **2b**), amber oil. UV (EtOH): ε (λ_{max}) = 3127 $dm^3\,mol^{-1}\,cm^{-1}$ (302 nm).[28] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.79–0.97 (m, 12 H), 1.08–1.69 (m, 24 H), 1.74–1.92 (m, 2 H), 2.07 (s, 3 H), 2.17 (s, 3 H), 2.67 (t, J = 6.6 Hz, 2 H), 3.23 (br. s, 2 H), 6.47 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.2, 15.9, 19.7, 19.8, 21.0, 22.7, 22.8, 23.8, 24.5, 24.8, 28.0, 31.7, 32.7, 32.8, 37.3, 37.5, 39.4, 39.7, 74.2, 116.5, 118.6, 119.7, 124.1, 136.0, 145.3 ppm. $[\alpha]_D^{23}$ = +5.6 (c = 1.0, EtOH). MS (APCI): m/z = 416.7 $[M+H]^+$. $C_{28}H_{49}NO$ (415.69): calcd. C 80.90, H 11.88, N 3.37; found C 81.02, H 11.91, N 3.44.

(2*R*,4′*R*,8′*R*)-γ-Tocopheramine (3d): Yield 345 mg (83% with respect to **3b**), amber oil. UV (EtOH): ε (λ_{max}) = 3345 $dm^3 mol^{-1} cm^{-1}$ (304 nm).[28] ^1H NMR (300 MHz, $CDCl_3$): δ = 0.83–0.98 (m, 12 H), 1.12–1.70 (m, 24 H), 1.75–1.88 (m, 2 H), 2.11 (s, 3 H), 2.18 (s, 3 H), 2.70 (t, J = 6.3 Hz, 2 H), 3.24 (br. s, 2 H), 6.34 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.8, 13.0, 19.6, 19.7, 20.9, 22.2, 22.5, 22.6, 24.0, 24.4, 24.7, 27.9, 31.5, 32.6, 32.7, 37.2, 37.4, 37.5, 39.3, 40.0, 75.1, 113.1, 118.2, 121.0, 124.8, 136.5, 144.9 ppm. $[\alpha]_D^{23}$ = +1.8 (c = 1.0, EtOH). MS (APCI): m/z = 416.6 $[M + H]^+$. $C_{28}H_{49}NO$ (415.69): calcd. C 80.90, H 11.88, N 3.37; found C 81.05, H 11.90, N 3.31.

(2*R*,4′*R*,8′*R*)-δ-Tocopheramine (4d): Yield 370 mg (92% with respect to **4b**), dark-amber oil. UV (EtOH): ε (λ_{max}) = 2863 $dm^3 mol^{-1} cm^{-1}$ (304 nm).[28] ^1H NMR (300 MHz, $CDCl_3$): δ = 0.81–0.96 (m, 12 H), 1.05–1.59 (m, 24 H), 1.69–1.83 (m, 2 H), 2.11 (s, 3 H), 2.66 (t, J = 6.6 Hz, 2 H), 3.13 (br. s, 2 H), 6.28 (d, J = 2.4 Hz, 1 H), 6.38 (d, J = 2.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.0, 19.6, 19.7, 20.9, 22.4, 22.6, 22.7, 24.1, 24.4, 24.8, 27.9, 31.4, 32.6, 32.7, 37.2, 37.4, 39.3, 39.8, 75.2, 113.2, 116.4, 121.0, 126.9, 138.0, 145.1 ppm. $[\alpha]_D^{23}$ = +5.7 (c = 1.0, EtOH). MS (APCI): m/z = 402.6 $[M + H]^+$. $C_{27}H_{47}NO$ (401.67): calcd. C 80.74, H 11.79, N 3.49; found C 80.89, H 11.82, N 3.43.

(2*R*,3′*E*,7′*E*)-α-Tocotrienamine (5d): Yield 310 mg (73% with respect to **5b**), amber oil. UV (EtOH): ε (λ_{max}) = 3435 $dm^3 mol^{-1} cm^{-1}$ (301 nm).[28] ^1H NMR (300 MHz, $CDCl_3$): δ = 1.32 (s, 3 H), 1.58–1.96 (m, 16 H), 2.00–2.29 (m, 19 H), 2.72 (t, J = 6.6 Hz, 2 H), 3.33 (br. s, 2 H), 5.20 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.0, 12.5, 13.6, 16.0, 16.1, 17.8, 21.1, 22.4, 23.8, 25.8, 26.7, 26.9, 32.0, 39.7, 39.8, 74.1, 117.1, 117.6, 120.4, 122.3, 124.3, 124.6, 124.7, 131.2, 134.9, 135.0, 144.8 ppm. $[\alpha]_D^{23}$ = –5.8 (c = 1.0, EtOH). MS (APCI): m/z = 424.7 $[M + H]^+$. $C_{29}H_{45}NO$ (423.67): calcd. C 82.21, H 10.71, N 3.31; found C 82.33, H 10.72, N 3.37.

(2*R*,3′*E*,7′*E*)-γ-Tocotrienamine (6d): Yield 336 mg (82% with respect to **6b**), amber oil. UV (EtOH): ε (λ_{max}) = 3175 $dm^3 mol^{-1} cm^{-1}$ (302 nm).[28] ^1H NMR (300 MHz, $CDCl_3$): δ = 1.22 (s, 3 H), 1.48–1.84 (m, 16 H), 1.90–2.21 (m, 16 H), 2.69 (t, J = 6.6 Hz, 2 H), 3.21 (br. s, 2 H), 5.13 (m, 3 H), 6.33 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.9, 13.1, 15.8, 16.0, 17.6, 22.1, 22.3, 24.0, 25.6, 26.6, 26.7, 31.5, 39.7, 39.8, 75.0, 113.2, 118.3, 121.1, 124.2, 124.4, 124.5, 125.0, 131.1, 134.8, 134.9, 136.6, 145.0 ppm. $[\alpha]_D^{23}$ = –6.8 (c = 1.0, EtOH). MS (APCI): m/z = 410.6 $[M + H]^+$. $C_{28}H_{43}NO$ (409.65): calcd. C 82.09, H 10.58, N 3.42; found C 82.22, H 10.52, N 3.47.

(2*R*,3′*E*,7′*E*)-δ-Tocotrienamine (7d): Yield 364 mg (92% with respect to **7b**), dark-amber oil. UV (EtOH): ε (λ_{max}) = 2796 $dm^3 mol^{-1} cm^{-1}$ (304 nm).[28] ^1H NMR (300 MHz, $CDCl_3$): δ = 1.23 (s, 3 H), 1.52–1.88 (m, 16 H), 1.92–2.20 (m, 13 H), 2.68 (t, J = 6.6 Hz, 2 H), 3.19 (br. s, 2 H), 5.12 (m, 3 H), 6.28 (d, J = 2.7 Hz, 1 H), 6.39 (d, J = 2.7 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.8, 15.9, 16.0, 17.6, 22.1, 22.3, 24.0, 25.6, 26.5, 26.7, 31.5, 39.6, 75.0, 113.2, 116.5, 121.0, 124.1, 124.3, 124.4, 126.9, 131.1, 134.8, 134.9, 138.0, 145.0 ppm. $[\alpha]_D^{23}$ = –1.6 (c = 1.0, EtOH). MS (APCI): m/z = 396.7 $[M + H]^+$. $C_{27}H_{41}NO$ (395.62): calcd. C 81.97, H 10.45, N 3.54; found C 82.12, H 10.51, N 3.62.

Supporting Information (see also the footnote on the first page of this article): Characterization data, including data for **1c**–**7c**, and chromatograms obtained by chiral HPLC.

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