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Biomimetic Chromanol Cyclisation: A Common Route to α-Tocotrienol and α-Tocopherol

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A common synthetic route to α-tocotrienol and α-tocopherol has been accomplished by a biomimetic cyclisation that yields the chromanol ring. The chirality at C2 of the chromanol was induced by a covalently attached chiral dipeptide. Its terminal Asp participates in the enantioface-selective protonation of the double bond of the α-tocotrienol precursor. α-Tocotrienol was diastereoselectively hydrogenated to α-tocopherol.

Introduction

Vitamin E comprises naturally occurring tocopherols **1**–**4** and tocotrienols **5**–**8** (Figure 1). The discovery of the enzyme tocopherol cyclase from *Cyanobacteria*[1] and investigations of its substrate specificity[2] and reaction mechanism[3] revealed that (i) the enzyme enables cyclisation of hydroquinone precursors with a phytyl side-chain (see **9**) and unsaturated side-chains to give **2** and **6**, respectively, with the same efficiency and (ii) the 42 kD protein operates by *Si* protonation of the double bond and concomitant *Re* attack of the phenol (Scheme 1).

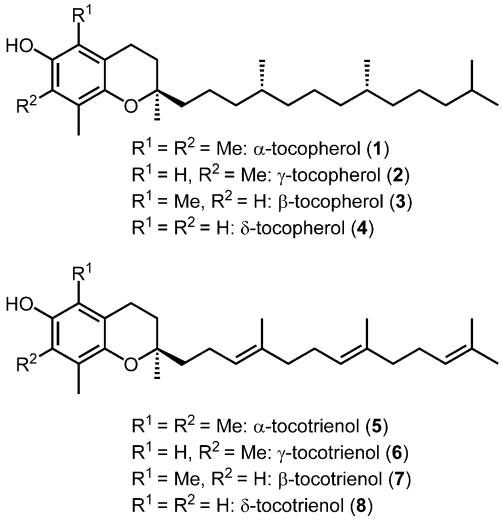

Figure 1. Structures of vitamin E compounds.

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In view of the weak acidity of the amino acids in the active site of the protein it was suggested[4] that substrates such as **9** bind to the enzyme in a high-energy conformation (Scheme 1), in which both the phenol and proton source are within binding distance of the double bond.

This insight led to a biomimetic synthesis of α-tocopherol (**1**) by using a large protecting group R and a dipeptide as steric constraints to generate a suitable conformation of the hydroquinone and to provide a proton source[4] (**10**; Scheme 2). We wish to report herein a similar approach to diastereomerically enriched α-tocotrienol (**5**) and α-tocopherol (**1**) in a convergent fashion.

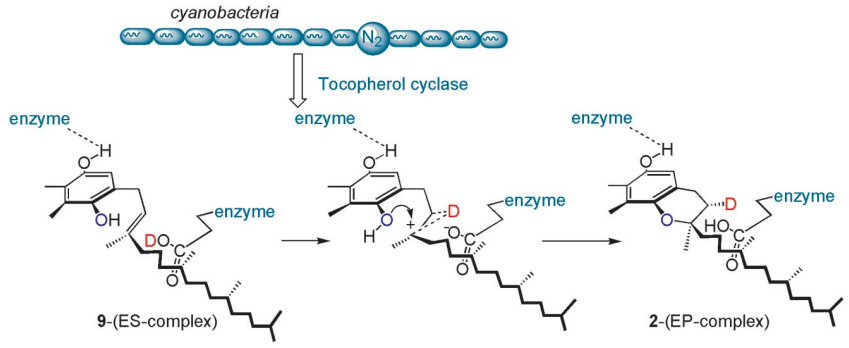
Results and Discussion

The synthesis of the precursor **D-11** was designed by analogy to the preparation of **10**[4] (Scheme 3). The chiral unit could be attached to the aromatic ring of **13** by a Mannich coupling reaction with the proline derivative **12** and was further derivatised by using a classical peptide synthesis.

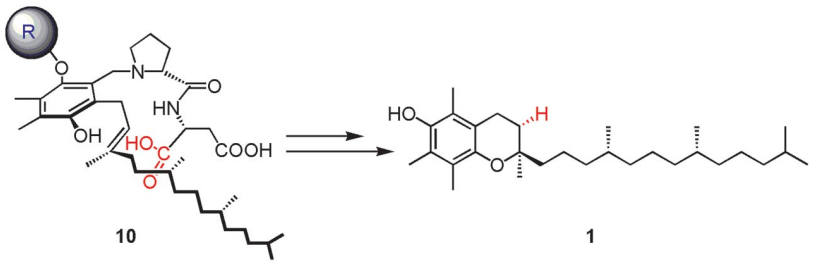
Finally, **13** could be obtained by aromatic substitution of the bis(protected) hydroquinone **14** with (all-*E*)-geranylgeranyl bromide (**15**) generated from 2,3-dimethylhydroquinone (**16**) and geranylgeraniol (**17**), respectively.

Synthesis of Precursor D-11

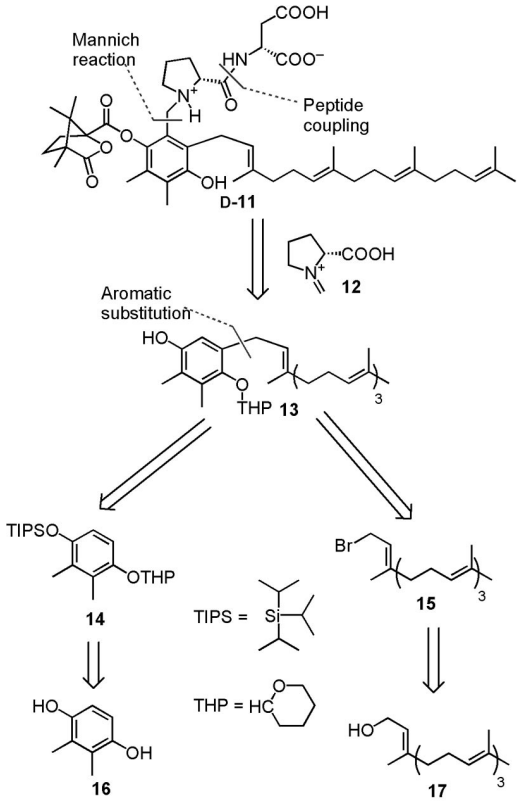
The synthesis of **D-11** started from the commercially available 2,3-dimethylhydroquinone (**16**), which was protected stepwise as the tetrahydropyranyl (THP) and triisopropylsilyl (TIPS) ethers to afford **14** in 42% overall yield (Scheme 4). By analogy to the synthesis reported by Klinge and Demuth,[5] (all-*E*)-farnesylacetone was converted into its unsaturated ester homologue by a Horner–Wadsworth–Emmons reaction and subsequently reduced by using



Scheme 1. Reaction mechanism of tocopherol cyclase.

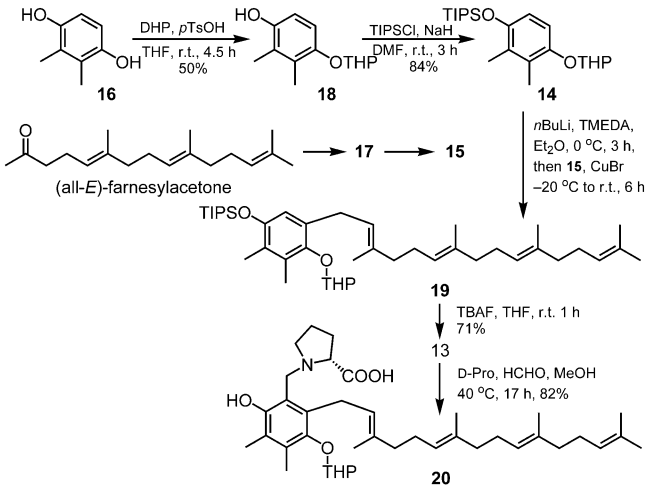


Scheme 2. Biomimetic approach to α-tocopherol (**1**).



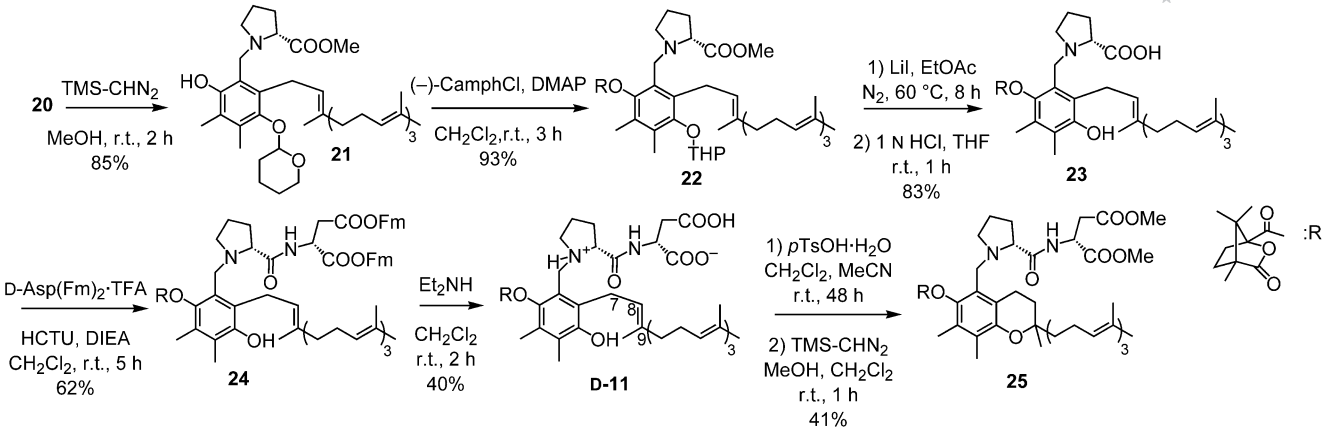
Scheme 3. Retrosynthetic approach to compound **D-11**.

DIBAL-H to furnish (all-*E*)-geranylgeraniol (**17**). The corresponding bromide **15** was directly coupled with the bis-(protected) hydroquinone **14** to afford **19**. The regioselectivity of the substitution adjacent to the THP group is directed by the coordination of the lithium cation to the THP oxygen atom. Owing to the difficulties involved in separating **19** and **14** the crude product **19** was treated with TBAF in THF to afford **13** in 71% from **14**.



Scheme 4. Synthesis of **20**.

From our previous work[4] with the phytylhydroquinone derivative **10**, it is known that cyclisation to the chromanol yields the (*R*) chirality at C2 only if the D-Pro–D-Asp peptide is employed as a chiral auxiliary. Consequently, the same strategy was used in this case and Mannich coupling of **13** with *N*-methylene-D-proline was pursued. The resulting prolinylphenol **20** was treated with trimethylsilyldiazomethane to yield the ester **21** to prevent intramolecular side-reactions during the following step (Scheme 5). Treatment of **21** with (–)-camphanoyl chloride furnished the es-



Scheme 5. Synthesis of precursor **D-11** and its biomimetic cyclisation.

ter **22** carrying a bulky substituent R (see **10**) adjacent to the chiral auxiliary, which is required to force the final dipeptide into a conformation that is close to the C8 double bond. Note that the chirality of the camphanoyl group is not significant to the diastereoselectivity of the cyclisation; however, this group facilitates the separation of diastereoisomers in consecutive steps.

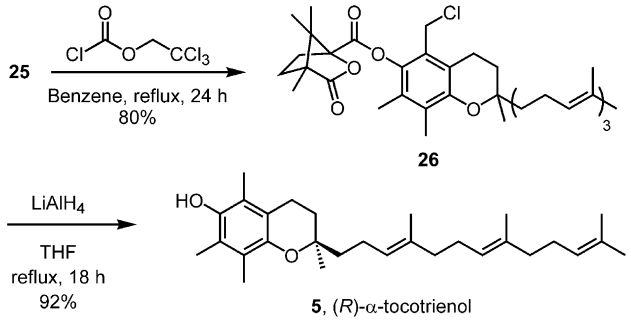
Hydrolysis of the prolinyl methyl ester proved to be difficult but was finally accomplished by using LiI under a constant flow of N_2 to eliminate the MeI formed, driving the reaction to completion. It was observed that the THP group was partially cleaved under these conditions; its hydrolysis was completed to afford **23** in 83% from **22**. Coupling of **23** with the TFA salt of Fm-protected D-aspartate yielded **24**, which was finally deprotected to give the geranylgeranylphenol **D-11** ready for cyclisation (Scheme 5).

Cyclisation of D-11

Treatment of **D-11** with 2 equiv. of pTsOH·H_2O at 25 °C for 48 h led to the desired chromanol ring as the major product together with unreacted starting material. Protonation of the side-chain double bonds must be a minor pathway as we could not isolate any tricyclic product arising from a cascade cyclisation, as described by Yamamoto and co-workers.[6] To facilitate isolation and purification, diester **25** was prepared directly from the crude mixture by using trimethylsilyldiazomethane. The selectivity of the cyclisation was determined at a later stage, as the separation of the C2 diastereoisomers was not possible for **25**.

Removal of Chiral Auxiliary – Synthesis of α-Tocotrienol (5)

The synthesis of α-tocotrienol (**5**) requires the removal of the chiral auxiliary. Reductive hydrogenation of the benzylamine unit is not compatible with substrate **25** due to the presence of double bonds in the side-chain. Several alternatives were envisaged, such as the Birch reduction,[7] but treatment of **25** with a mixture of Li (1% Na) in $EtNH_2$/THF (20:1) did not afford the desired product in sufficient quantity. The von Braun reaction[8] seemed to be a promising method and has been reported to be unreactive towards olefins. However, the original reaction conditions using cyanogen bromide failed; **25** was recovered unchanged. Finally, the use of chloroformate[9] gave satisfactory results, and treatment of **25** with an excess of 2,2,2-trichlorethyl chloroformate afforded the corresponding benzyl chloride **26** in 80% yield (Scheme 6). In contrast, reactions with benzyl and allyl chloroformates were sluggish.

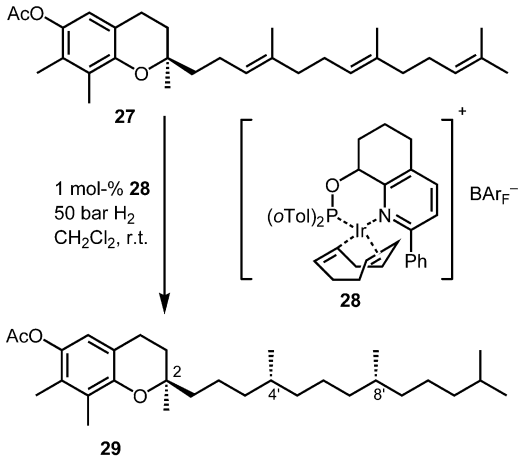


Scheme 6. Cleavage of the chiral auxiliary – synthesis of α-tocotrienol (**5**).

Treatment of **26** with $LiAlH_4$ led to the simultaneous reduction of the benzyl chloride and the (–)-camphanate ester, yielding (2*R*)-α-tocotrienol (**5**) in 92% yield and 65% *ee*.[10] This value corresponds to the diastereoisomeric excess observed in the reaction depicted in Scheme 2.[4]

Asymmetric Hydrogenation – Synthesis of α-Tocopherol (1)

Recently, Pfaltz and co-workers reported the use of the chiral iridium catalyst **28** for the asymmetric hydrogenation of isolated olefins.[11] A remarkable example of this investigation was the hydrogenation of (2*R*)-γ-tocotrienyl acetate (**27**), which afforded (2*R*,4′*R*,8′*R*)-γ-tocopheryl acetate (**29**) in more than 98% *de* (Scheme 7).



Scheme 7. Asymmetric hydrogenation of γ-tocotrienyl acetate (**27**).[11]

Iridium catalyst **28** was therefore employed in the catalytic hydrogenation of enantiomerically enriched α-tocotrienyl acetate (**30**), derived from **5** (Scheme 8). Hydrogenation proceeded smoothly to afford α-tocopheryl acetate (**31**), which was subsequently reduced to α-tocopherol (**1**).

The ratio of the eight possible stereoisomers was determined by a combination of HPLC analysis of **1** and GC analysis of α-tocopheryl methyl ether (**32**) developed by Walther and Netscher.[12] An excellent (*R*)/(*S*) ratio of up to >99:1 at C4′ and C8′ in favour of the (*R*) configuration was observed.

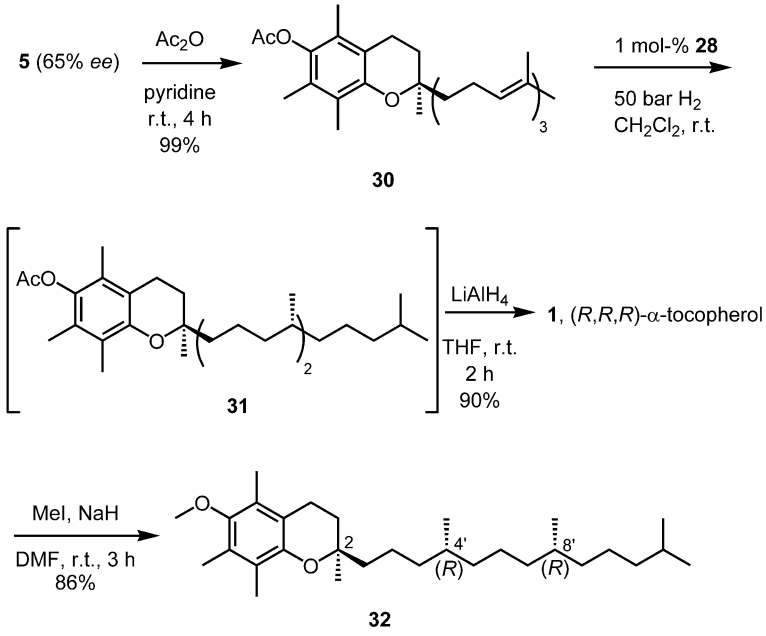
The synthetic route depicted in Scheme 5 was also pursued with L-Pro–L-Asp as the chiral auxiliary. Precursor **L-11** was obtained in similar yields, and its cyclisation gave predominantly the (2*S*)-configured α-tocotrienol (**5**; 73% *ee*). Subsequent acetylation and hydrogenation afforded (*S*,*R*,*R*)-α-tocopherol (**1**) in an (*R*)/(*S*) ratio of up to >99:1 at C4′ and C8′. These results confirm the influence of the peptide configuration on the cyclisation and demonstrate the high selectivity of the iridium catalyst **28**, which is independent of the configuration at C2[11] and tolerates an additional methyl group on the aromatic ring.

Conclusions

The diastereofacial protonation of the isolated double bond of a geranylgeranylhydroquinone derivative has been accomplished with a proline–aspartate dipeptide attached to the aromatic ring. Addition of the phenol to the protonated double bond furnished the chromanol system of α-tocotrienol. A chiral iridium complex was then used to catalyse the hydrogenation of the double bonds of α-tocotrienol to give α-tocopherol with excellent diastereoselectivity. This procedure allows for the biomimetic synthesis of two important members of the vitamin E family by a common route.

Experimental Section

General Remarks: Unless stated otherwise, reactions were performed in flame-dried glassware under a positive pressure of argon. Chemicals and solvents were purchased from commercial suppliers and purified by standard techniques whenever necessary. For thin-layer chromatography (TLC), silica gel plates (Merck AG $60F_{254}$) were used and compounds were visualised by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid, cerium(IV) sulfate and concd. H_2SO_4 in water (2:4:40:160, wt/wt) followed by heating. Flash chromatography was performed by using Merck silica gel 60 (particle size 0.040–0.063 mm). ^1H and ^{13}C NMR spectra were recorded with a Bruker DPX NMR (400 and 500 MHz) spectrometer at 25 °C. Chemical shifts δ are given



Scheme 8. Asymmetric hydrogenation of α-tocotrienyl acetate (**30**).

in ppm relative to tetramethylsilane (TMS), and the coupling constants *J* are given in Hz. The spectra were recorded in $CDCl_3$ as solvent (δ = 7.26 ppm for ^1H, δ = 77.2 ppm for ^{13}C). HPLC was carried out by using an LC-20AB pump, an SPD-M20A detector and an SIL-20A autosampler (Shimadzu) with Chiracel OD-H column. Microanalyses were performed with a Perkin-Elmer 240 Analyser. IR spectra recorded with a Shimadzu FTIR-8400S spectrometer.

Mono-THPO-hydroquinone 18:[4] 2,3-Dihydropyran (16.7 mL, 183.1 mmol) was added to a solution of 2,3-dimethylhydroquinone (**16**; 23.0 g, 166.5 mmol) in THF (150 mL) at –5 °C, followed by *p*-tosylOH·H_2O (285.2 mg, 1.50 mmol), and the mixture was stirred at 25 °C for 5 h. The reaction was quenched with saturated $NaHCO_3$ and the mixture extracted with TBME (3×). The combined organic phases were washed with H_2O and then brine (2×), dried with Na_2SO_4, concentrated to dryness, and the residue was purified by column chromatography on SiO_2 (hexane/EtOAc, 83:17) to afford **18** (18.6 g, 50%) as a light-orange solid. M.p. 92–94 °C. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.60–1.70 (m, 3 H, CH_2-THP), 1.85–1.95 (m, 2 H, CH_2-THP), 1.95–2.05 (m, 1 H, CH_2-THP), 2.17 (s, 3 H, 2/3-CH_3), 2.20 (s, 3 H, 2/3-CH_3), 3.62–3.65 (m, 1 H, CH_2-THP), 3.90–3.98 (m, 1 H, CH_2-THP), 4.42 (s, 1 H, OH), 5.24 (t, *J* = 3.3 Hz, 1 H, C*H*-THP), 6.56 (d, *J* = 8.7 Hz, 1 H, H_{Ar}), 6.84 (d, *J* = 8.7 Hz, 1 H, H_{Ar}) ppm.

THPO-TIPSO-hydroquinone 14:[4] NaH (60% on mineral oil, 517.0 mg, 13.0 mmol) was added to a solution of **18** (2.63 g, 11.8 mmol) in THF (150 mL) at 0 °C, and the mixture was stirred for 10 min. Triisopropylsilyl chloride (3.0 mL, 14.2 mmol) was added dropwise at 0 °C and the mixture further stirred at 25 °C for 3 h. The reaction was quenched with saturated $NaHCO_3$ and the mixture extracted with TBME (3×). The combined organic phases were dried with Na_2SO_4, concentrated to dryness, and the residue was purified by column chromatography on SiO_2 (hexane/EtOAc, 97:3) to afford **14** (3.77 g, 84%) as a white solid. M.p. 34–35 °C. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.10 (d, *J* = 6.5 Hz, 18 H, CH_3-TIPS), 1.21–1.33 (m, 3 H, C*H*-TIPS), 1.60–1.70 (m, 3 H, CH_2-THP), 1.84–1.95 (m, 2 H, CH_2-THP), 1.95–2.05 (m, 1 H, CH_2-THP), 2.17 (s, 3 H, 2/3-CH_3), 2.18 (s, 3 H, 2/3-CH_3), 3.57–3.62 (m, 1 H, CH_2-THP), 3.91–4.00 (m, 1 H, CH_2-THP), 5.23 (t, *J* = 3.3 Hz, 1 H, C*H*-THP), 6.57 (d, *J* = 8.8 Hz, 1 H, H_{Ar}), 6.79 (d, *J* = 8.8 Hz, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 13.0, 13.4, 18.5, 19.6, 25.8, 31.2, 62.6, 97.9, 115.0, 115.4, 127.8, 128.3, 149.1, 149.5 ppm. $C_{22}H_{38}O_3Si$ (378.62): calcd. C 69.79, H 10.12; found C 70.00, H 10.12. IR (KBr): $\tilde{\nu}_{max}$ = 2942, 2866, 1540, 1477, 1384, 1247, 1091, 1038, 923, 883 cm^{-1}. UV (CH_2Cl_2): λ_{max} = 238, 286 nm.

(all-*E*)-Geranylgeraniol (17): Triethyl phosphonoacetate (2 mL, 10.0 mmol) was slowly added to a suspension of NaH (60% in mineral oil, 430 mg, 10.8 mmol) in THF (25 mL) and the mixture was stirred at 25 °C for 1 h. Farnesylacetone (1.86 g, 7.1 mmol) in THF (3 mL) was then added and the mixture further stirred for 16 h. The reaction was quenched with cold saturated brine, the mixture extracted with EtOAc, and the organic phase was washed with H_2O, dried with Na_2SO_4, and the solvents were evaporated to dryness. The residue was purified by column chromatography on SiO_2 (hexane/Et_2O, 95:5) to afford (all-*E*)-geranylgeranoyl ethyl ester (1.48 g, 66%) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.27 (t, *J* = 7.1 Hz, 3 H, Et), 1.60 (s, 9 H, CH_3C=C), 1.68 (s, 3 H, CH_3C=C), 1.90–2.20 (m, 15 H, CH_3C=C, CH_2), 4.14 (q, *J* = 7.2 Hz, 2 H, Et), 5.02–5.12 (m, 3 H, C*H*=C), 5.66 (s, 3 H, C=C*H*COOEt) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.7, 16.4, 18.1, 19.2, 26.1, 26.4, 27.0, 27.2, 40.1, 41.4, 59.8, 116.0, 123.3, 124.5, 124.8, 131.7, 135.4, 136.6, 160.2, 167.3 ppm. GC [Optima-5 PhMe Si column, 25 m × 0.2 mm, 0.35 μm; split injector (1:20), injector temp. 250 °C; FID detector, detector temp. 270 °C, carrier gas: H_2, 20 psi; 100–270 °C (6 °C/min), 39 min]: $t_{(Z,E,E,E)}$ = 26.6 min, $t_{(E,E,E,E)}$ = 27.4 min, (*E*)/(*Z*) > 99:1. DIBAL-H (0.7–1.3 M in hexane, 10.0 mL) was added dropwise to a solution of the (all-*E*)-geranylgeranoyl ethyl ester (1.67 g, 5.25 mmol) in Et_2O (20 mL) at 0 °C and the reaction mixture was further stirred at 25 °C for 2 h. The reaction was quenched by the addition of H_2O at 0 °C, the mixture extracted with EtOAc, and the organic phase was washed with H_2O, dried with Na_2SO_4, and the solvents were evaporated to dryness. The residue was passed through a pad of SiO_2 (EtOAc) to afford (all-*E*)-geranylgeraniol (**17**; 1.1 g, 72%) as a slightly yellow oil. The spectral data were identical to those previously reported.[13] Selected data: ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.60 (s, 9 H, CH_3C=C), 1.68 (s, 6 H, CH_3C=C), 1.90–2.15 (m, 12 H, CH_2), 4.15 (t, *J* = 6.1 Hz, 2 H, CH_2OH), 5.03–5.15 (m, 3 H, C*H*=C), 5.42 (m, 1 H, C=C*H*CH_2OH) ppm.

Monoprotected Hydroquinone 13: TMEDA (1.7 mL, 11.4 mmol) and **14** (4.3 g, 11.4 mmol) in Et_2O (10 mL) were added to a solution of *n*BuLi (1.6 M in hexane, 7.4 mL, 11.8 mmol) in Et_2O (40 mL) at 0 °C. The mixture was stirred at 0 °C for 3 h and then cooled to –20 °C. CuBr (530 mg, 3.6 mmol) was added followed by geranylgeranyl bromide (**15**;[14] 3.2 g, 9.11 mmol) in Et_2O (10 mL), and the mixture was stirred at 25 °C for 6 h. The reaction was quenched with saturated $NaHCO_3$ and the mixture extracted with TBME (3×). The combined organic phases were dried with Na_2SO_4, concentrated to dryness, and the residue was purified by column chromatography on SiO_2 (hexane/CH_2Cl_2, 75:25) to afford a mixture of **19** and **14** (5.33 g). TBAF (1 M in THF, 10.5 mL, 10.5 mmol) was added to the mixture of **19** and **14** (5.33 g) in THF (70 mL), and the mixture was stirred at 25 °C for 1 h. The reaction was quenched with saturated $NaHCO_3$ and the mixture extracted with TBME (3×). The combined organic phases were dried with Na_2SO_4, concentrated to dryness, and the residue was purified by column chromatography on SiO_2 (CH_2Cl_2) to afford **13** (3.20 g, 71% over two steps) as a slightly yellow oil. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.48–1.63 (m, 12 H, 3′/4′-H, 9/13/17-CH_3), 1.66–1.70 (dd, *J* = 5.7, 1.0 Hz, 6 H, 21-CH_3), 1.77–1.87 (m, 1 H, 5′-H), 1.90–2.02 (m, 6 H, 14/18/3′/4′-H), 2.02–2.16 (m, 6 H, 10/11/15/19-H), 2.12 (s, 3 H, 2-CH_3), 2.21 (s, 3 H, 3-CH_3), 3.36 (d, *J* = 7.3 Hz, 2 H, 7-H), 3.40–3.47 (m, 1 H, 2′-H), 4.00–4.19 (m, 1 H, 2′-H), 4.49 (s, 1 H, OH), 4.61–4.69 (m, 1 H, 1′-H), 5.05–5.17 (m, 3 H, 12/16/20-H), 5.29 (t, *J* = 6.9 Hz, 1 H, 8-H), 6.44 (s, 1 H, 6-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 11.9, 12.2, 14.0, 15.9, 16.0, 16.1, 17.6, 21.1, 25.1, 25.6, 26.5, 26.7, 28.4, 31.2, 39.6, 39.7, 65.1, 103.7, 112.9, 120.8, 122.8, 124.1, 124.3, 131.2, 132.7, 134.9, 136.1, 147.8, 149.6 ppm. MS (ESI, MeOH): *m*/*z* = 571.4 [M + Na]$^+$. IR (neat): $\tilde{\nu}_{max}$ = 3401, 2922, 2852, 1442, 1379, 1200, 1074, 1034, 954, 910, 833, 651 cm^{-1}. UV (MeOH): λ_{max} = 209, 285 nm.

D-ProOH Derivative 20: A solution of D-proline (4.6 g, 39.9 mmol) in formaldehyde (35% aq., 3.3 mL, 41.9 mmol) was stirred at 40 °C under a flow of N_2 for 15 min. The viscous white solid was dissolved in MeOH (15 mL), and **13** (959.7 mg, 1.94 mmol) was added in MeOH (7 mL). The mixture was stirred at 40 °C for 17 h and then cooled to 25 °C. The reaction was quenched with saturated $NaHCO_3$ and the mixture extracted with CH_2Cl_2 (3×). The combined organic phases were dried with Na_2SO_4, concentrated to dryness, and the residue was purified by column chromatography on SiO_2 (CH_2Cl_2/MeOH, 90:10) to afford **20** (989 mg, 82%) as a pink oil. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.45–1.63 (m, 12 H, 3′/4′-H, 9/13/17/21-CH_3), 1.67 (s, 3 H, 9/13/17/21-CH_3), 1.71–1.84 (m, 1 H, 5′-H), 1.75 (s, 3 H, 9/13/17/21-CH_3), 1.84–2.00 (m, 8 H,

14/18/3′/4′/4′′-H), 2.00–2.10 (m, 6 H, 10/11/15/19-H), 2.11–2.31 (m, 7 H, 2/3-CH_3, 3′′-H), 2.30–2.44 (m, 1 H, 3′′-H), 2.73–2.82 (m, 1 H, 5′′-H), 3.25–3.52 (m, 3.5 H, 7/2′/5′′-H), 3.52–3.57 (m, 0.5 H, 7-H), 3.72–3.80 (m, 1 H, 6′′-H), 3.83–4.03 (m, 2 H, 2′/1′′-H), 4.35–4.42 (m, 1 H, 1′′-H), 4.55–4.62 (m, 1 H, 1′-H), 5.00–5.16 (m, 4 H, 8/12/16/20-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 12.9, 14.4, 14.5, 15.9, 16.0, 16.5, 17.6, 21.2, 23.5, 25.0, 25.6, 26.5, 26.7, 31.2, 39.6, 65.2, 65.4, 103.9, 123.7, 123.8, 124.0, 124.3, 131.2, 134.9, 135.0, 135.3, 147.4 ppm. MS (ESI, MeOH): *m*/*z* = 622.8 $[M + H]^+$, 644.5 $[M + Na]^+$. $C_{39}H_{59}NO_5$ (621.90): calcd. C 75.32, H 9.56, N 2.25; found C 74.84, H 9.29, N 2.18. IR (neat): $\tilde{\nu}_{max}$ = 2920, 2851, 1619, 1450, 1377, 1251, 1202, 1074, 1033, 907, 645, 587 cm^{-1}. UV (MeOH): λ_{max} = 207, 290 nm.

D-ProOMe Derivative 21: Trimethylsilyldiazomethane (2 M in hexane, 8.1 mL, 16.29 mmol) was added dropwise to a solution of **20** (779.6 g, 1.25 mmol) in MeOH (50 mL) at 25 °C. The mixture was stirred for 2 h, the reaction quenched with saturated $NaHCO_3$ and the mixture extracted with CH_2Cl_2 (3×). The combined organic phases were dried with Na_2SO_4, concentrated to dryness, and the residue was purified by column chromatography on SiO_2 (CH_2Cl_2/MeOH, 99.5:0.5) to afford **21** (677.4 mg, 85%) as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.45–1.64 (m, 12 H, 3′/4′-H, 9/13/17/21-CH_3), 1.67 (s, 3 H, 9/13/17/21-CH_3), 1.74 (s, 3 H, 9/13/17/21-CH_3), 1.76–1.89 (m, 2 H, 5′-H), 1.89–2.00 (m, 8 H, 14/18/4′/3′′/4′′-H), 2.01–2.10 (m, 6 H, 10/11/15/19-H), 2.16 (s, 3 H, 2-CH_3), 2.17–2.26 (m, 4 H, 3-CH_3, 3′′-H), 2.34 (m, 1 H, 4′′-H), 3.04 (m, 1 H, 4′′-H), 3.24–3.34 (m, 2 H, 7-H), 3.36–3.55 (m, 2 H, 2′/2′′-H), 3.61 (dd, *J* = 13.4, 8.5 Hz, 1 H, 1′′-H), 3.74 (s, 3 H, CH_3O), 3.93 (dd, *J* = 13.4, 10.83 Hz, 1 H, 1′′-H), 3.98–4.05 (m, 1 H, 2′-H), 4.61 (d, *J* = 8.0 Hz, 1 H, 1′-H), 4.97–5.15 (m, 4 H, 8/12/16/20-H), 10.68 (s, 1 H, OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 11.9, 14.1, 15.9, 16.5, 17.6, 21.3, 23.2, 25.1, 25.6, 25.7, 25.9, 26.6, 26.7, 29.5, 31.2, 39.6, 52.1, 52.5, 52.9, 53.2, 65.1, 65.2, 65.5, 65.7, 104.0, 104.1, 117.8, 117.9, 122.2, 124.0, 124.3, 129.9, 131.2, 134.3, 134.8, 134.9, 135.0, 146.4, 152.4, 173.8 ppm. MS (ESI, MeOH): *m*/*z* = 636.6 $[M + H]^+$, 658.4 $[M + Na]^+$. $C_{40}H_{61}NO_5$ (635.93): calcd. C 75.55, H 9.67, N 2.20; found C 75.38, H 9.42, N 2.03. IR (neat): $\tilde{\nu}_{max}$ = 2919, 2850, 1741, 1438, 1377, 1250, 1203, 1076, 1033 cm^{-1}. UV (MeOH): λ_{max} = 224, 289 nm.

(–)-CamphanoylO-/THPO-D-ProOMe Derivative 22: DMAP (432 mg, 3.54 mmol) followed by (–)-camphanoyl chloride (831 mg, 3.84 mmol) were added to a solution of **21** (642.6 mg, 1.01 mmol) in CH_2Cl_2 (40 mL) at 25 °C. The mixture was stirred for 3 h, the reaction quenched with saturated $NaHCO_3$ and the mixture extracted with CH_2Cl_2 (3×). The combined organic phases were dried with Na_2SO_4, concentrated to dryness, and the residue was purified by column chromatography on SiO_2 (CH_2Cl_2/MeOH, 99:1) to afford **22** (769.0 mg, 93%) as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.10–1.22 (m, 9 H, 5′′′/7′′′-CH_3), 1.46–1.63 (m, 12 H, 3′/4′-H, 9/13/17/21-CH_3), 1.67 (s, 3 H, 9/13/17/21-CH_3), 1.69–1.87 (m, 7 H, 9/13/17/21-CH_3, 5′/3′′/4′′′-H), 1.88–2.00 (m, 9 H, 11/14/15/18/19/4′/5′/4′′-H), 2.00–2.12 (m, 11 H, 2-CH_3, 10/11/15/19/3′′/4′′′-H), 2.18–2.33 (m, 4 H, 3-CH_3, 3′′′-H), 2.36–2.70 (m, 2 H, 5′′/3′′′-H), 2.72–3.00 (m, 1 H, 5′′-H), 3.12–3.17 (m, 0.5 H, 2′′-H), 3.24–3.54 (m, 4.5 H, 7/2′/1′′/2′′/7′′-H), 3.54–3.95 (m, 4 H, 7/1′′/7′′-H), 3.96–4.06 (m, 1 H, 2′-H), 4.71 (d, *J* = 5.8 Hz, 1 H, 1′-H), 4.97–5.13 (m, 4 H, 8/12/16/20-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 9.63, 13.7, 14.5, 15.9, 16.5, 17.0, 17.6, 21.1, 25.0, 25.6, 26.6, 26.7, 28.9, 31.2, 31.4, 39.6, 54.8, 64.4, 65.1, 90.9, 103.9, 124.1, 124.3, 126.6, 131.1, 134.8 ppm. MS (ESI, MeOH): *m*/*z* = 816.6 $[M + H]^+$, 838.5 $[M + Na]^+$. $C_{50}H_{73}NO_8$ (816.13): calcd. C 73.59, H 9.02, N 1.72; found C 72.82, H 8.72, N 1.65. IR (neat): $\tilde{\nu}_{max}$ = 2921, 2852, 1795, 1748, 1448, 1377, 1261, 1232, 1166, 1063, 1033, 632, 534 cm^{-1}. UV (MeOH): λ_{max} = 208, 270 nm.

(–)-CamphanoylO-/HO-D-ProOH Derivative 23: LiI (3.3 g, 24.6 mmol) was added to a solution of **22** (733.0 mg, 0.90 mmol) in EtOAc (7 mL). The solution was stirred at 60 °C under a flow of N_2 (addition of EtOAc, ca. 3 mL/h) for 8 h, and then the reaction was quenched with saturated $NaHCO_3$ and the mixture extracted with CH_2Cl_2 (3×). The combined organic phases were dried with Na_2SO_4, concentrated to dryness, and the residue was filtered through a pad of SiO_2 (CH_2Cl_2/MeOH, 99:1) to afford a crude oil (574.8 mg), which was used directly without further purification. The crude material was dissolved in THF (60 mL), and 1 N $HCl_{aq.}$ (30 mL) was added. The mixture was stirred for 1 h at 25 °C. The reaction was quenched with saturated $NaHCO_3$ and the mixture extracted with CH_2Cl_2 (3×). The combined organic phases were dried with Na_2SO_4, concentrated to dryness, and the residue was purified by column chromatography on SiO_2 (CH_2Cl_2/MeOH, 99:1) to afford **23** (531.4 mg, 83% over two steps) as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.11–1.21 (m, 9 H, 5′′/7′′-CH_3), 1.54–1.63 (m, 9 H, 9/13/17/21-CH_3), 1.67 (s, 3 H, 9/13/17/21-CH_3), 1.73–1.89 (m, 5 H, 9/13/17/21-CH_3, 4′′-H), 1.91–2.01 (m, 6 H, 14/18/4′-H), 2.01–2.13 (m, 11 H, 2-CH_3, 10/11/15/19-H), 2.17 (s, 3 H, 3-CH_3), 2.21–2.33 (m, 2 H, 3′/3′′-H), 2.50–2.62 (m, 1 H, 3′′-H), 2.75–3.02 (m, 1 H, 5′-H), 3.35–3.42 (m, 1 H, 5′-H), 3.42–3.61 (m, 2 H, 7-H), 3.62–3.75 (m, 1 H, 2′-H), 3.75–4.07 (m, 2 H, 1′-H), 5.00–5.20 (m, 4 H, 8/12/16/20-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 9.6, 12.5, 13.7, 15.9, 16.0, 16.4, 16.7, 17.1, 17.6, 24.3, 25.5, 25.6, 26.2, 26.3, 26.5, 26.7, 28.6, 29.6, 31.1, 39.5, 39.6, 54.8, 90.1, 90.7, 120.5, 123.3, 124.1, 124.3, 128.1, 131.1, 134.9, 135.7, 140.2, 151.8, 165.9, 177.5 ppm. MS (ESI, MeOH): *m*/*z* = 718.6 $[M + H]^+$, 740.5 $[M + Na]^+$, 756.3 $[M + K]^+$. $C_{44}H_{63}NO_7$ (717.98): calcd. C 73.61, H 8.84, N 1.95; found C 72.55, H 8.86, N 1.80. IR (neat): $\tilde{\nu}_{max}$ = 3537, 2916, 2853, 1794, 1755, 1635, 1448, 1381, 1311, 1240, 1161, 1090, 1034, 845, 735 cm^{-1}. UV (MeOH): λ_{max} = 205, 288 nm.

(–)-CamphanoylO-/HO-D-Pro-D-Asp(Fm)$_2$ Derivative 24: A solution of **23** (506.0 mg, 0.705 mmol) and HCTU (1.1 g, 2.61 mmol) in CH_2Cl_2 (20 mL) was stirred at 25 °C for 0.5 h. Then D-Asp(Fm)$_2$·TFA (850.0 mg, 1.41 mmol) and DIEA (730 μL, 4.23 mmol) were added, and the mixture was stirred at 25 °C for 5 h. The reaction was quenched with saturated NH_4Cl and the mixture extracted with CH_2Cl_2 (3×). The combined organic phases were dried with Na_2SO_4, concentrated to dryness, and the residue was purified by column chromatography on SiO_2 (CH_2Cl_2/MeOH, 95:5) to afford **24** (512.4 mg, 62%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.07–1.22 (m, 9 H, 5′′/7′′-CH_3), 1.49–1.62 (m, 9 H, 9/13/17/21-CH_3), 1.67 (s, 3 H, 9/13/17/21-CH_3), 1.69–1.86 (m, 5 H, 9/13/17/21-CH_3, 4′′-H), 1.86–2.34 (m, 23 H, 2/3-CH_3, 10/11/14/15/18/19/3′/4′/3′′-H), 2.35–2.70 (m, 3 H, 5′/3′′-H), 2.70–2.98 (m, 2 H, 10′-H), 3.02–3.84 (m, 6 H, 7/1′/2′-H), 4.09–4.20 (m, 2 H, 12′-H), 4.25–4.55 (m, 4 H, 11′-H), 4.75–4.90 (m, 1 H, 8′-H), 4.93–5.15 (m, 4 H, 8/12/16/20-H), 5.21 (s, 1 H, OH), 7.19–7.43 (m, 7 H, Fm-H_{Ar}), 7.46–7.60 (m, 4 H, Fm-H_{Ar}), 7.64–7.79 (m, 4 H, Fm-H_{Ar}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 9.6, 12.2, 13.5, 15.9, 16.0, 16.2, 16.8, 16.9, 17.6, 25.5, 25.6, 26.2, 26.5, 26.7, 28.8, 35.8, 39.5, 39.6, 46.5, 51.3, 54.7, 66.8, 70.5, 119.9, 121.1, 123.3, 124.1, 124.3, 124.9, 127.0, 127.2, 127.7, 131.1, 134.8, 135.7, 141.1, 143.4, 143.5, 151.2, 170.8 ppm. MS (ESI, MeOH): *m*/*z* = 1190.7 $[M + H]^+$, 1212.3 $[M + Na]^+$, 1227.8 $[M + K]^+$. $C_{76}H_{88}N_2O_{10}$ (1189.54): calcd. C 76.74, H 7.46, N 2.36; found C 76.12, H 7.51, N 2.22. IR (neat): $\tilde{\nu}_{max}$ = 3365, 2966, 2914, 1792, 1738, 1668, 1506, 1448, 1263, 1227, 1163, 1092, 1047, 739 cm^{-1}.

(–)-CamphanoylO-/HO-D-Pro-D-Asp(OH)$_2$ Derivative D-11: Et_2NH (2.5 mL) was added to a solution of **24** (153.6 mg, 0.129 mmol) in CH_2Cl_2 (10 mL), and the mixture was stirred at 25 °C for 2 h. The solvents were removed in vacuo, and the crude product was dissolved in CH_2Cl_2 and extracted with $KHSO_4$ (100 mg in 5 mL H_2O). The aqueous phase was washed with CH_2Cl_2 (3×), and the combined organic phases were dried with Na_2SO_4, concentrated to dryness, and the residue was purified by column chromatography on SiO_2 (CH_2Cl_2/MeOH, 75:25) to afford **D-11** (42.9 mg, 40%) as a colourless oil. ^{1}H NMR (600 MHz, DMSO, 25 °C): δ = 0.96 (s, 3 H, 5′′/7′′-CH_3), 1.00 (s, 3 H, 5′′/7′′-CH_3), 1.06–1.15 (s, 3 H, 5′′/7′′-CH_3), 1.44–1.51 (m, 9 H, 9/13/17/21-CH_3), 1.51–1.73 (m, 8 H, 9/13/17/21-CH_3, 3′/4′/4′′-H), 1.78–2.00 (m, 16 H, 3-CH_3, 10/11/14/15/18/19/3′/4′-H), 2.00–2.33 (m, 6 H, 2-CH_3, 3′′/4′′-H), 2.33–2.45 (m, 1 H, 5′-H), 2.46–2.62 (m, 1 H, 5′-H), 2.62–2.78 (m, 0.2 H, 8′-H), 2.93–3.63 (m, 7 H, 7/1′/2′/5′/10′-H), 3.69–4.17 (m, 0.8 H, 8′-H), 4.87–5.12 (m, 4 H, 8/12/16/20-H), 7.44–7.84 (m, 1 H, NH), 7.98–8.68 (m, 2 H, OH) ppm. ^{13}C NMR (125 MHz, DMSO, from 2D exp. HMQC/HMBC, 25 °C): δ = 9.1, 12.7, 13.0, 15.4, 16.2, 16.3, 17.2, 23.6, 25.1, 25.8, 26.2, 27.9, 30.8, 38.8, 39.1, 47.6, 49.9, 52.8, 53.9, 54.4, 55.3, 64.2, 66.4, 90.7, 123.7, 124.7, 125.6, 127.5, 130.6, 134.3, 140.7, 150.9, 177.8 ppm. MS (ESI, MeOH): *m*/*z* = 834.0 [M + H]$^+$, 856.0 [M + Na]$^+$, 877.9 [M + 2Na]$^+$, 832.0 [M – H]$^-$. IR (neat): $\tilde{\nu}_{max}$ = 3353, 2968, 2918, 1795, 1751, 1595, 1423, 1416, 1238, 1163, 1091, 1048, 930 cm^{-1}. UV (MeOH): λ_{max} = 240, 284 nm.

(–)-Camphanoyl-D-Pro-D-Asp(OMe)$_2$ Cyclised Derivative 25: *p*-TosylOH·H_2O (16.3 mg, 85.7 μmol) in ACN (2 mL) was added to a solution of **D-11** (34.0 mg, 40.82 μmol) in CH_2Cl_2 (35 mL), and the mixture was stirred at 25 °C for 48 h. The reaction was quenched with saturated $NaHCO_3$ and the mixture extracted with CH_2Cl_2 (3×). The combined organic phases were dried with Na_2SO_4, concentrated to dryness, and the crude oil was dried under high vacuum. The residue was then dissolved in MeOH/CH_2Cl_2 (4:1, 2.5 mL), and trimethyldiazomethane (2 M in hexane, 0.6 mL, 1.2 mmol) was added. The mixture was stirred at 25 °C for 1 h, and the reaction was quenched with saturated $NaHCO_3$ and the mixture extracted with CH_2Cl_2 (3×). The combined organic phases were dried with Na_2SO_4, concentrated to dryness and purified by column chromatography on SiO_2 (CH_2Cl_2/MeOH, 98.5:1.5) to afford **25** (15.2 mg, 41% over two steps) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.10–1.32 (m, 9 H, 5′′′/7′′′-CH_3), 1.49–1.89 (m, 23 H, 2/4′/8′/12′-CH_3, 3/1′/3′′′/4′′/4′′′-H), 1.89–2.31 (m, 19 H, 7/8-CH_3, 2′/5′/6′/9′/10′/3′′/3′′′/4′′′-H), 2.35–3.42 (m, 9 H, 4/2′′/5′′/10′/3′′′/4′′′-H), 3.53–3.89 (m, 8 H, COOCH_3, 1′′-H), 4.53–4.99 (m, 1 H, 8′′-H), 5.00–5.23 (m, 3 H, 3′/7′/11′-H), 7.68–8.17 (m, 1 H, NH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, from 2D exp. HMQC/HMBC, 25 °C): δ = 9.6, 12.2, 13.5, 17.0, 17.3, 21.3, 23.0, 25.5, 25.7, 28.7, 28.9, 30.8, 35.3, 39.4, 39.7, 52.2, 53.9, 55.2, 59.5, 61.4, 63.1, 64.6, 69.3, 74.2, 75.4, 77.2, 77.4, 85.7, 89.3, 90.8, 92.6, 124.3, 131.2, 134.9, 141.2, 143.2, 171.4, 178.1 ppm. MS (ESI, MeOH): *m*/*z* = 861.8 [M + H]$^+$, 883.7 [M + Na]$^+$. IR (neat): $\tilde{\nu}_{max}$ = 3365, 2921, 2853, 1794, 1739, 1674, 1502, 1436, 1376, 1225, 1163, 1092, 1044 cm^{-1}. $C_{50}H_{72}N_2O_{10}$ (861.13): calcd. C 69.74, H 8.43, N 3.25; found C 69.23, H 8.36, N 3.15. Determination of the diastereoisomeric excess by HPLC analysis was not possible at this stage, peaks were not properly resolved.

Benzyl Chloride 26: 2,2,2-Trichlorethyl chloroformate (135.2 mg, 0.64 mmol) was added to a solution of **25** (18.4 mg, 21.4 μmol) in benzene (2 mL). The solution was heated at reflux for 24 h, and the mixture was then cooled to 25 °C. The reaction was quenched with saturated $NaHCO_3$ and the mixture extracted with CH_2Cl_2 (3×). The combined organic phases were dried with Na_2SO_4, concentrated to dryness and purified by column chromatography on SiO_2 (CH_2Cl_2) to afford **26** as a colourless oil. (10.9 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.14–1.29 (m, 9 H, 5′′/7′′-CH_3), 1.50–1.72 (m, 18 H, 2/4′/8′/12′-CH_3, 1′/4′′-H), 1.72–1.91 (m, 4 H, 3/5′/9′-H), 1.89–2.16 (m, 15 H, 7/8-CH_3, 2′/5′/6′/9′/10′/4′′-H), 2.25–2.34 (m, 1 H, 3′′-H), 2.55–2.70 (m, 1 H, 3′′-H), 2.77–2.85 (m, 2 H, 4-H), 4.36–4.67 (m, 2 H, CH_2Cl), 5.05–5.17 (m, 3 H, 3′/7′/11′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 9.6, 12.2, 13.2, 15.8, 15.9, 16.8, 17.6, 19.1, 22.0, 25.6, 26.5, 26.6, 28.9, 29.2, 30.6, 31.4, 37.8, 39.6, 54.3, 54.9, 75.3, 91.1, 117.9, 123.9, 124.0, 124.3, 127.4, 131.2, 134.9, 135.3, 150.0, 166.0, 177.9 ppm. MS (ESI, MeOH): *m*/*z* = 661.5 [M + Na]$^+$, 675.3 [M + HCl]$^+$.

α-Tocotrienol (5): $LiAlH_4$ (1 M in THF, 0.150 mmol) was added to a solution of **26** (38.1 mg, 59.8 μmol) in THF (2.5 mL), and the mixture was heated at reflux for 18 h. The reaction was quenched with H_2O/1 N HCl and the mixture extracted with Et_2O (3×). The combined organic phases were dried with Na_2SO_4, concentrated to dryness and purified by column chromatography on SiO_2 (CH_2Cl_2) to afford **5** as a colourless oil (23.4 mg, 92%). The spectral data were identical to those of an original sample. Selected data: ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 1.26 (s, 3 H, 2-CH_3), 1.57–1.70 (m, 14 H, 1′-H, 4′/8′/12′-CH_3), 1.75–1.87 (m, 2 H, 3-H), 1.90–2.20 (m, 19 H, 5/7/8-CH_3, 2′/5′/6′/9′/10′-H), 2.61 (t, *J* = 6.8 Hz, 2 H, 4-H), 4.20 (s, 1 H, OH), 5.05–5.18 (m, 3 H, 3′/7′/11′-H) ppm.

α-Tocotrienyl Acetate (30): Acetic anhydride (400 μL) was added to a solution of α-tocotrienol (**5**; 23.4 mg, 55.0 μmol) in pyridine (2 mL), and the mixture was stirred at 25 °C for 4 h. The reaction was quenched with 1 N HCl and the mixture extracted with CH_2Cl_2 (3×). The combined organic phases were dried with Na_2SO_4, concentrated to dryness and purified by column chromatography on SiO_2 (CH_2Cl_2) to afford **30** as a colourless oil (25.7 mg, >99%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.26 (s, 3 H, 2-CH_3), 1.57–1.70 (m, 14 H, 1′-H, 4′/8′/12′-CH_3), 1.75–1.87 (m, 2 H, 3-H), 1.92–2.18 (m, 19 H, 5/7/8-CH_3, 2′/5′/6′/9′/10′-H), 2.33 [s, 3 H, CH_3(CO)-O], 2.60 (t, *J* = 6.6 Hz, 2 H, 4-H), 5.05–5.22 (m, 3 H, 3′/7′/11′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 11.7, 12.0, 12.8, 15.8, 15.9, 17.6, 20.5, 22.1, 25.6, 26.5, 26.7, 39.6, 74.7, 91.1, 117.2, 123.0, 124.1, 124.3, 126.6, 131.2, 134.9, 135.0, 140.4, 149.3, 169.6 ppm. MS (ESI, MeOH): *m*/*z* = 489.6 [M + Na]$^+$, 505.4 [M + K]$^+$.

α-Tocopherol (1): The iridium catalyst **28** (0.55 μmol) was added to a solution of **30** (25.7 mg, 55.0 μmol) in CH_2Cl_2 (0.5 mL), and the mixture was stirred at 25 °C under 50 bar of H_2 for 3 h. The solvent was removed in vacuo, and hexane (1 mL) was added. The solids were filtered off (0.45 μm filter) and washed with hexane. The solvent was removed in vacuo, and the crude colourless oil was used directly in the next step. The crude oil was dissolved in THF (1 mL), and $LiAlH_4$ (1 M in THF, 0.38 mmol) was added. The mixture was stirred at 25 °C for 2 h. The reaction was quenched with H_2O and the mixture extracted with Et_2O (3×). The combined organic phases were dried with Na_2SO_4 and concentrated to dryness to afford α-tocopherol as a colourless oil (21.3 mg, 90%). The crude material was used without further purification. The spectral data were identical to those of an original sample. Selected data: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.80–0.91 (m, 12 H, 4′/8′/12′-CH_3), 0.97–1.57 (m, 24 H, 2-CH_3, 1′/2′/3′/4′/5′/6′/7′/8′/9′/10′/11′/12′-H), 1.70–1.83 (m, 2 H, 3-H), 2.11 (s, 6 H, 5/7/8-CH_3), 2.16 (s, 3 H, 5/7/8-CH_3), 2.60 (t, *J* = 6.9 Hz, 2 H, 4-H), 4.19 (s, 1 H, OH) ppm. HPLC (Chiracel OD-H, 0.5% EtOH in *n*-hexane, 1 mL/min, 25 °C, 220 nm): $t_{(2R,4'RS,8'RS)}$ = 7.9 min (79.8%), $t_{(2S,4'RS,8'RS)}$ = 9.0 min (16.7%).

α-Tocopheryl Methyl Ether (32): To a suspension of NaH (60% in mineral oil, 2.9 mg, 74.0 μmol) in DMF (0.5 mL) at 0 °C was added a solution of **1** (21.3 mg, 49.5 μmol) in DMF (1 mL). The mixture was stirred at 0 °C for 30 min, and MeI (7 μL, 59.0 μmol) was added. The solution was warmed to 25 °C and stirred for 3 h. The reaction was quenched with a saturated $NaHCO_3$ solution and the mixture extracted with CH_2Cl_2 (3 ×). The combined organic phases were dried with Na_2SO_4, concentrated to dryness, and the residue was purified by column chromatography on SiO_2 (hexane/EtOAc, 9:1) to afford **32** as a colourless oil (18.9 mg, 86%). The spectral data were identical to those previously reported.[15] Selected data: ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.85 (d, J = 6.6 Hz, 3 H, 4′/8′-CH_3), 0.86 (d, J = 6.6 Hz, 3 H, 4′/8′-CH_3), 0.87 (d, J = 6.6 Hz, 6 H, 12′-CH_3), 0.90–1.19 (m, 7 H, 2′/3′/5′/6′/7′/9′/10′-H), 1.23 (s, 3 H, 2-CH_3), 1.19–1.47 (m, 13 H, 1′/2′/3′/4′/5′/6′/7′/8′/9′/10′/11′-H), 1.48–1.53 (m, 1 H, 12′-H), 1.70–1.83 (m, 2 H, 3-H), 2.09 (s, 3 H, 5-CH_3), 2.14 (s, 3 H, 8-CH_3), 2.18 (s, 3 H, 7-CH_3), 2.58 (t, J = 6.8 Hz, 2 H, 4-H), 3.63 (s, 3 H, CH_3O) ppm. GC [CP-Sil-88 column, 50 m × 0.25 mm, 0.25 μm; split injector (1:30), injector temp. 280 °C; FID detector, detector temp. 250 °C, carrier gas: H_2, 90 kPa; 170 °C, 140 min]: $t_{(R,R,S/S,S,R)}$ = 136.9 min (1.29%), $t_{(R,R,R/S,S,S)}$ = 138.9 min (80.4%), $t_{(R,S,R/S,R,S)}$ = 140.7 min (1.29%), $t_{(R,S,S/S,R,R)}$ = 144.9 min (17.0%); (*R*,*R*,*R*) = 80.4%, (*S*,*R*,*R*) = 17.0%, (*R*,*S*,*S*) ≈ 0%, (*S*,*S*,*S*) ≈ 0%, (*R*,*R*,*S*) = 1.06%, (*R*,*S*,*R*) = 1.06%, (*S*,*S*,*R*) = 0.23%, (*S*,*R*,*S*) = 0.23%.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra and the numbering of all new intermediates.

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