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Asymmetric Synthesis of α-Tocopherol

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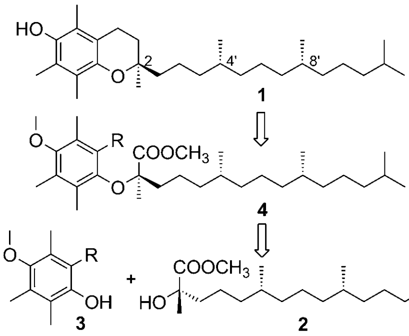
Dedicated to Professor André Dreiding on the occasion of his 90th birthday

Abstract: α-Tocopherol was synthesized from a chiral intermediate α-hydroxy ester by means of two ring-closing methods to yield the chromanol in 94 % diastereomeric excess.

Keywords: asymmetric synthesis · chromanes · enantioselectivity · tocopherol · vitamin E

Introduction

α-Tocopherol (**1**) is the biologically most significant member of the vitamin E family and is known to act as a very efficient radical-chain-breaking antioxidant in tissues.[1] The isolation of pure **1** (Scheme 1) from all photosynthetic organisms is quite difficult, because the compound appears in various amounts along with other vitamin E chromanols. The challenge to prepare enantiomerically enriched **1** results from the presence of stereogenic centers at C2, C4′, and C8′.



Scheme 1. General strategy for the synthesis of α-tocopherol (**1**).

Results and Discussion

A comprehensive review by Netscher describes the syntheses of racemic and enantiomerically enriched tocopherols and chromanols until 2006.[2] Since then several very efficient methods to prepare α-tocopherol (**1**) have been published.[3]

We wish to report here a further unprecedented approach that uses the chiral key intermediate **2** in Mitsunobu reactions with various phenols **3** to generate chiral phenol ethers **4** that could be further elaborated for the preparation of **1** (Scheme 1). The α-hydroxy ester **2** was chosen, because in model reactions of one of phenols **3a–c** with one of nitrile **5a**, olefin **5b**, or propargyl alcohol **5c**, the Mitsunobu reactions were unsatisfactory and gave ethers **6a–h** in yields below 20 % (Scheme 2).

Accordingly, it was concluded that activation by the COOR group[4] was necessary to accomplish clean Mitsunobu reactions with inversion of configuration.

For the synthesis of hydroxy ester **2**, two chiral units were required: 1) Grignard reagent **7**, available from (*R*,*R*)-hexahydrofarnesol **8**[5] via bromide **9**, and 2) epoxide **10** (Scheme 3). The latter was prepared from β-methylallyl alcohol by a Sharpless epoxidation protocol[6] that yielded crystalline *p*-nitrobenzoate **11** (94 % *ee*), which was hydrolyzed to **10a** and subsequently reacted with EtMgCl to furnish **10b**, the magnesium salt of methyl glycidol. The reaction between **7** and **10b** catalyzed by lithium cuprate[7]gave the *S*,*R*,*R*-configured diol **12** in 75 % yield. Oxidation of the primary alcohol function[8] of **12** led to chiral hydroxy ester **2** in 91 % yield.

The general strategy was then to use **2** as a Mitsunobu reactant with phenols **13**, **14**, and **15** to provide tertiary ethers **16**, **17**, and **18** under inversion of configuration (Scheme 4).[4] From **16**, **17**, and **18**, three options A, B, and

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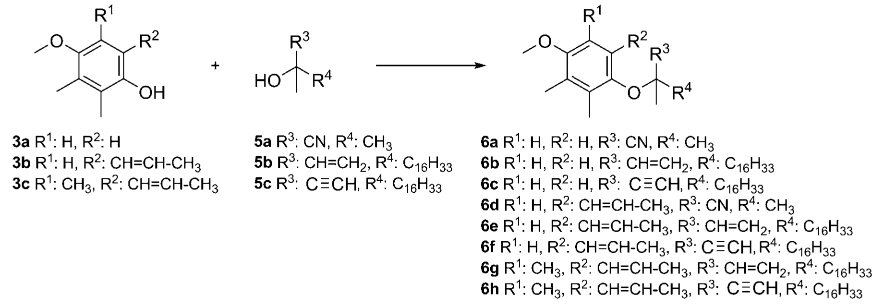
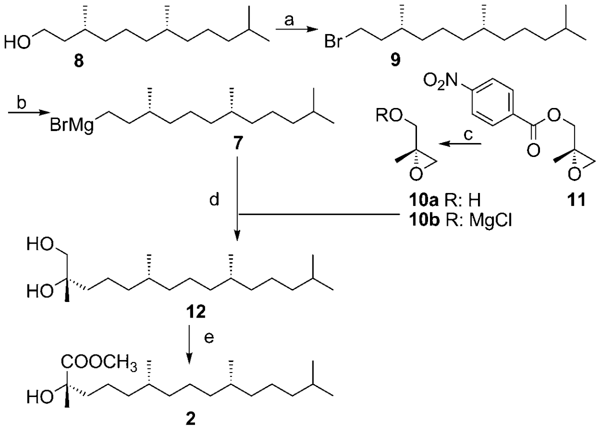
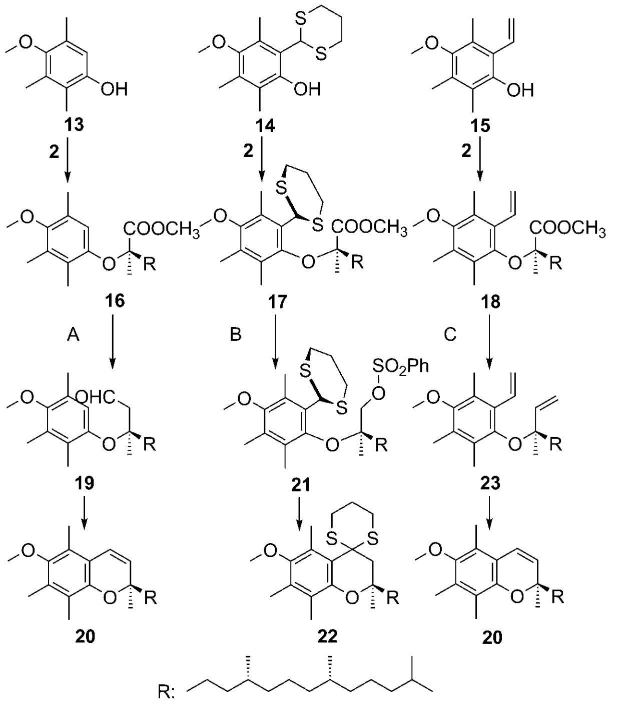


Scheme 2. Attempted Mitsunobu reactions of monoprotected hydroquinones **3a–c** with various tertiary alcohols **5**.



Scheme 3. Synthesis of key intermediate **2**. Experimental conditions: a) PPh$_3$, NBS, CH$_2$Cl$_2$, 98%; b) Mg, THF, RT; c) i. LiOH, THF/H$_2$O, RT, 81%; ii. EtMgCl, THF; d) Li$_2$CuCl$_4$, THF, −78°C to RT, 75%; e) i. NaClO$_2$, TEMPO, NaOCl, MeCN/aq phosphate buffer, 55°C; ii. MeOH, HCl, RT, 91%.

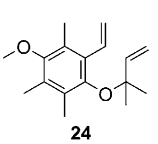


Scheme 4. Coupling of various phenols with key intermediate **2** and possible further reactions towards chromenes and chromanes.

C can be envisaged to ring-close these compounds to chiral chromanes or chromenes. Ester **16** could be transformed into aldehyde **19**, which could cyclize to form chromene **20** under acidic conditions (route A; Scheme 4).

Alternatively, **17** could give sulfonate **21**, which was expected to ring-close to chromane **22** in a nucleophilic displacement after deprotonation with *n*BuLi (route B; Scheme 4). The third possibility, transformation of ester **18** into a vinyl group would generate a bis-olefin **23**, suitable for a metathesis reaction leading to chromene **20** (route C).

Route C was abandoned because model reactions with **24** and **25**(in the presence of various highly active metathesis catalysts[9] such as [1,3-bis(2-methylphenyl)-2-imidazolidinylidene]dichloro(benzylidene)(tricyclohexylphosphine)ruthenium(II) or [1,3-bis(2-methylphenyl)-2-imidazolidinylidene]dichloro(2-isopropoxyphenylmethylene)ruthenium(II) failed to give the chromene system in yields greater than 25%. Hence routes A and B were pursued for the synthesis of α-tocopherol.



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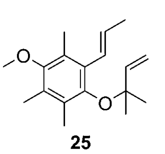

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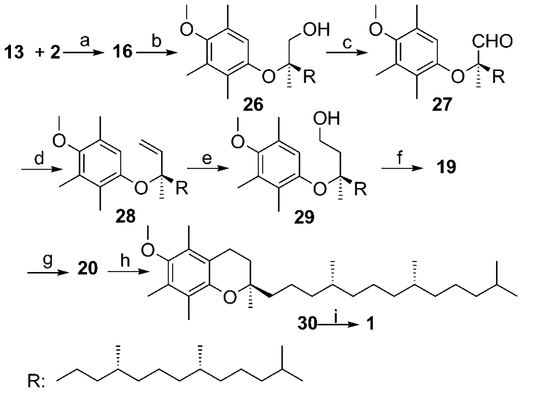
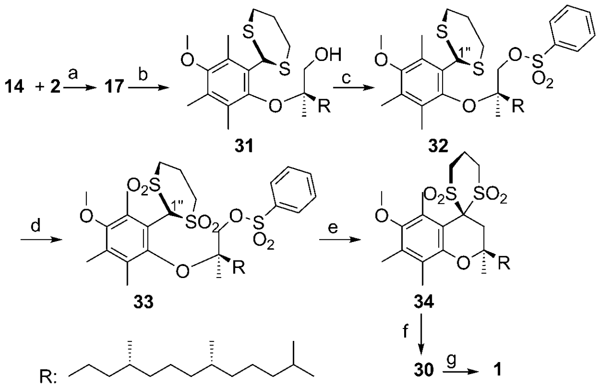
As for route A (Scheme 5), the monoprotected hydroquinone **13** reacted with hydroxy ester **2** under modified Mitsunobu conditions[4] to give ether **16** with complete inversion of configuration [94% diastereomeric excess (*de*)] and in acceptable 64% yield. Quantitative reduction of **16** furnished alcohol **26**, which was oxidized to aldehyde **27**. Homologation to **28** and subsequent rhodium-catalyzed hydroboration[10] gave alcohol **29** in excellent yield.

Since direct ring closure of **29** to α-tocopheryl methyl ether **30** according to Trost[10] proved to be moderate in yield and reproducibility, we chose a two-step procedure (Scheme 5). Hence, **29** was oxidized to aldehyde **19**, which was—without prior isolation—treated with trifluoroacetic acid (TFA) to provide chromene **20** in 82% yield. Finally, catalytic hydrogenation gave chromane **30** in 94% *de*. Efficient deprotection of **30** to give α-tocopherol (**1**) has been reported by us before.[3d]



Scheme 5. Completing the synthesis of **1** by route A. Experimental conditions: a) DIAD, PPh_3, toluene, 100 °C, 64 %; b) $LiAlH_4$, THF, 0 °C, 100 %; c) Dess–Martin periodinane, CH_2Cl_2, RT, 92 %; d) $MePPh_3Br$, *n*BuLi, THF, 0 °C, 94 %; e) i. catecholborane, $RhCl(PPh_3)_3$, THF, RT; ii. $NaOH/H_2O_2$, 91 %; f) Dess–Martin periodinane, CH_2Cl_2, RT; g) TFA, RT, 82 %; h) H_2, Pd/C, EtOAc, 95 %; i) $BF_3{\cdot}SMe_2$, $AlCl_3$, MeCN, CH_2Cl_2, RT, 84 %.



Scheme 6. Completing the synthesis of **1** by route B. Experimental conditions: a) DIAD, PPh_3, toluene, RT, 68%; b) $LiAlH_4$, THF, 0 °C, 100%; c) $PhSO_2Cl$, pyridine, RT, 84%; d) *m*CPBA, CH_2Cl_2, RT, 94%; e) NaOMe, MeOH, RT, 98%; f) i. lithium naphthalenide, THF, −78 °C; ii. MeOH; iii. lithium naphthalenide, THF, −78 °C, 86%; g) $BF_3{\cdot}SMe_2$, $AlCl_3$, MeCN, CH_2Cl_2, RT, 84%.

Route B of the plan was executed by using thioacetal **14** and hydroxy ester **2** for the Mitsunobu reaction (Scheme 6). The condensation product **17** was isolated in 68 % yield and subsequently reduced to alcohol **31**. According to Seebach,[11] the benzenesulfonate is the best leaving group for the anticipated cyclization. Hence **32** was prepared and treated with *n*BuLi to provide **22**. To our dismay, this reaction did not work at all. Surprisingly, in a quenching experiment with D_2O we did not observe deuteration at C1″ of **32**.

Since deprotonation of **32** did not work, we decided to oxidize the thioacetal to the sulfone in order to use a different and milder deprotonation method.[12] Indeed, after oxidation of **32**, the resulting bis-sulfone **33**, on treatment with NaOMe, smoothly cyclized to form chromane **34** in 98 % yield (Scheme 6). Reductive removal of the dithiane tetroxide moiety was finally achieved with the use of excess lithium naphthalenide in THF at −78 °C; chromane **30** (94 % *de*) was isolated in 86 % yield.

Conclusion

New strategies for the synthesis of α-tocopherol (**1**) were developed by using a chiral α-hydroxy ester for stereospecific Mitsunobu reactions and subsequent elaboration of two cyclization methods towards the chromanol system. Throughout the syntheses, the diastereomeric excess of the α-hydroxy ester (94 % *de*) was retained.

Experimental Section

General: Chemicals and solvents were purchased from commercial suppliers or purified by standard techniques. For TLC, silica gel plates (Merck AG $60F_{254}$) were used and compounds were visualized 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 by weight) followed by heating. Flash chromatography was performed by using Fluka silica gel 60 (particle size 0.040–0.063 mm). ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX-NMR (400 MHz and 500 MHz) spectrometer at ambient temperature. Chemical shifts are given in δ relative to tetramethylsilane, and the coupling constants J are given in Hz. The spectra were recorded in $CDCl_3$ as solvent at ambient temperature, tetramethylsilane served as internal standard ($\delta = 0$ ppm) for ^1H NMR spectra and $CDCl_3$ was used as internal standard ($\delta = 77.2$ ppm) for ^{13}C NMR spectra. Melting points are uncorrected. IR spectroscopy was performed on a Perkin–Elmer 1600 FTIR apparatus. Electron-spray ionization mass spectra (ESI-MS) were recorded on a Bruker Esquire 3000 plus spectrometer. HPLC was carried out by using an intelligent pump, detector, and integrator on a Hewlett Packard S1100 or a Shimadzu LC-20AB/SPD-M20A instrument. Microanalyses were performed by use of a Perkin–Elmer 240 Analyser by Mr. W. Kirsch at the Department of Chemistry, University of Basel. Optical rotations were measured on a Perkin–Elmer Polarimeter 341 at $\lambda = 589$ nm.

(*S*)-(2-Methyloxiran-2-yl)methyl 4-nitrobenzoate (11): By following a literature procedure,[6] compound **11** was prepared by epoxidation of 2-methallyl alcohol with *tert*-butyl hydroperoxide and catalytic amounts of titanium(IV) isopropoxide and (−)-diethyl D-tartrate and subsequent acylation with *p*-nitrobenzoyl chloride. Colorless crystals; m.p. 85.8–86.6 °C (85.5–86.5 °C[6]); $[\alpha]_D^{20} = +4.4$ ($c = 0.9$ in $CHCl_3$); 94 % *ee*; HPLC [Chiralpak AD-H column (*n*-heptane/2-propanol 85:15), UV 254 nm, 0.6 mL min^{-1}]: major enantiomer $t_R = 16.7$ min ((*S*)-**11**), minor enantiomer $t_R = 17.7$ min ((*R*)-**11**); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.20$–8.32 (m, 4H), 4.56 (d, $J = 12$ Hz, 1H), 4.23 (d, $J = 12$ Hz, 1H), 2.86 (d, $J = 4$ Hz, 1H), 2.75 (d, $J = 4$ Hz, 1H), 1.47 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 164.67$, 151.09, 135.48, 131.25, 124.03, 68.95, 55.10, 52.26, 18.86 ppm; IR (neat): $\tilde{\nu} = 1715$ cm^{-1}; ESI-MS: *m/z*: 260 $[M+Na]^+$; elemental analysis calcd (%) for $C_{11}H_{11}NO_5$ (237.21): C 55.70, H 4.67, N 5.90; found: C 55.45, H 4.60; N 5.79

(*R*)-(2-Methyloxiran-2-yl)methanol (10a): A solution of lithium hydroxide monohydrate (1.26 g, 30 mmol) in water (10 mL) was added to an ice-cold solution of methylglycidol ester **11** (4.75 g, 20 mmol) in THF (30 mL); the two-phase mixture was vigorously stirred at room temperature for 30 min. The reaction mixture was diluted with CH_2Cl_2/Et_2O (2:1; 200 mL) and cooled in an ice bath. Anhydrous $MgSO_4$ (20 g) was added, and the mixture was stirred for 20 min and then filtered. The filtrate was concentrated to one tenth of its volume and dried again with $MgSO_4$ and molecular sieve powder (4 Å, < 5 µ). After removal of the solid material, the filtrate was concentrated and the residual oil was distilled at 75 °C/

21 mbar to give **10a** (1.43 g, 81 %) as a colorless oil. $[\alpha]_D^{20}=+11.1$ ($c=0.9$ in $CHCl_3$); a sample was acylated with *p*-nitrobenzoyl chloride/NEt_3 in dichloromethane and the isolated ester **11** analyzed by chiral HPLC as above: 94 % *ee*; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=3.72$ (dd, $J=12$, 4 Hz, 1H), 3.60 (dd, $J=12$, 8 Hz, 1H), 2.91 (d, 1H, $J=5$ Hz), 2.65 (d, $J=5$ Hz, 1H), 1.89 (dd, $J=8$, 4 Hz; H/D-exchange with D_2O), 1.35 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=64.6$, 57.7, 51.4, 18.5 ppm.

(3*R*,7*R*)-Hexahydrofarnesyl bromide (9): *N*-Bromosuccinimide (NBS; 4.63 g, 26 mmol) was added portionwise over 30 min to a solution of **8** (5.25 g, 23 mmol)[5] and triphenylphosphine (7.23 g, 27.6 mmol) in dichloromethane (35 mL) at 4–8 °C. The reaction mixture was stirred for 20 min and then concentrated on a rotary evaporator. The two-phase residue was triturated with hexane and the solid material was removed by filtration and washed with hexane. The concentrated filtrate was purified by chromatography (silica gel, hexane) to afford **9** (6.55 g, 98 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta=3.37$–3.50 (m, 2H), 1.85–1.95 (m, 1H), 1.02–1.72 (m, 16H), 0.83–0.90 ppm (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=40.45$, 39.76, 37.68, 37.66, 37.24, 33.17, 32.66, 32.09, 28.39, 25.20, 24.63, 23.13, 23.03, 20.14, 19.41 ppm; elemental analysis calcd (%) for $C_{15}H_{31}Br$ (291.31): C 61.85, H 10.73; found: C 62.00, H 10.61.

(2*S*,6*R*,10*R*)-2,6,10,14-Tetramethyl-1,2-pentadecanediol (12): 1,2-Dibromoethane (25 μL, 0.30 mmol) was added to a suspension of magnesium turnings (150 mg, 6.17 mmol) in THF (1.5 mL). After the mixture had stirred at 25–35 °C for 15 min, the solvent was removed by syringe and the magnesium turnings were suspended again in THF (1.5 mL). A solution of **9** (1.55 g, 5.32 mmol) in THF (7 mL) was added over 1 h and the mixture was stirred at room temperature for 8 h. In a second flask a solution of (*R*)-**10a** (423 mg, 4.80 mmol) in THF (7 mL) was cooled to −78 °C and the alcohol function was deprotonated by dropwise addition of a 2 M solution of ethylmagnesium chloride in THF (2.5 mL, 5.0 mmol). The solution of **10b** was stirred at −78 °C for 10 min, after which the Grignard reagent of **7**, prepared as described above, was added. The reaction mixture was stirred in the dry ice/acetone bath for 5 min. A catalytic amount of a 0.1 M solution of dilithium tetrachlorocuprate(II) in THF (0.40 mL, 40 μmol) was added. After stirring of the mixture for 5 min, the cooling bath was removed and the reaction mixture was allowed to warm to 25 °C while additional dilithium tetrachlorocuprate solution (0.80 mL, 80 μmol) was added during the warm-up period. The resulting black mixture was stirred at 25 °C overnight and finally quenched with half-saturated aq NH_4Cl and extracted with TBME (*tert*-butyl methyl ether); the organic layer was washed with brine, dried ($MgSO_4$), and concentrated on a rotary evaporator. The colorless oil was purified by chromatography (silica gel, *n*-hexane/EtOAc 1:1) to yield **12** (1.084 g, 75 %) as a colorless viscous oil. $[\alpha]_D^{20}=-0.9$ ($c=1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=3.47$ (*d*, $J=11$ Hz, 1H), 3.40 (*d*, $J=11$ Hz, 1H), 1.99 (s, 2H, O-H), 1.02–1.57 (m, 21H), 1.16 (s, 3H), 0.83–0.88 ppm (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=73.44$, 70.22, 39.77, 39.45, 38.01, 37.83, 37.79, 37.68, 33.19, 33.18, 28.38, 25.20 24.89, 23.67, 23.13, 23.03, 21.60, 20.15, 20.10 ppm; IR (neat): $\tilde{\nu}=3371$ cm^{-1}. ESI-MS: *m/z*: 323.5 $[M+Na]^+$, 623.7 $[2M+Na^+]$.

(2*S*,6*R*,10*R*)-2-Hydroxy-2,6,10,14-tetramethylpentadecanoic acid methyl ester (2): Sodium chlorite (750 mg, 6.63 mmol), 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO; 187 mg, 1.20 mmol), and a catalytic amount of 0.15 M aq sodium hypochlorite (0.60 mL, 90 μmol) were added to diol **12** (1.10 g, 3.66 mmol) in acetonitrile (25 mL) and 0.66 M phosphate buffer (pH 6.55, 18 mL). Then the two-phase mixture was stirred at 55 °C for 6 h. After addition of water (30 mL), the pH was adjusted to 11–12 with 2 N aq NaOH and the mixture was treated at room temperature with a solution of sodium sulfite (1.6 g) in water (30 mL) for 15 min. The mixture was acidified with 2 N aq HCl (pH 1–2) and extracted twice with EtOAc. The combined EtOAc phases were washed with brine, dried ($MgSO_4$), and concentrated on a rotary evaporator. The crude carboxylic acid was taken up in 2 M HCl in methanol (25 mL) and stirred at 25 °C overnight. The mixture was partitioned between TBME and half-saturated brine, and the organic phase was washed with brine containing a small amount of $NaHCO_3$, dried ($MgSO_4$), and concentrated on a rotary evaporator. The residual colorless oil was purified by chromatography (silica gel, *n*-hexane/EtOAc 10:1) to yield **2** (1.099 g, 91 %) as a colorless viscous oil. $[\alpha]_D^{20}=+8.2$ ($c=1.2$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=3.78$ (s, 3H), 3.12 (br s, 1H), 1.67–1.76 (m, 1H), 1.0–1.63 (m, 20), 1.40 (s, 3H), 0.81–0.87 ppm (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$ 178.21, 75.10, 53.11, 40.90, 39.77, 37.82, 37.69, 37.38, 33.20, 33.03, 28.38, 26.52, 25.20, 24.86, 23.13, 23.03, 21.55, 20.15, 19.92 ppm; IR (neat): $\tilde{\nu}=3530$, 1732 cm^{-1}; ESI-MS: *m/z*: 351.3 $[M+Na]^{++}$, 679.4 $[2M+Na]^+$; elemental analysis calcd (%) for $C_{20}H_{40}O_3$ (328.53): C 73.12, H 12.27; found: C 72.98, H 12.14.

(2*R*,6*R*,10*R*)-2-(4-Methoxy-2,3,5-trimethylphenoxy)-2,6,10,14-tetramethylpentadecanoic acid methyl ester (16): A solution of α-hydroxy ester **2** (1.303 g, 4.0 mmol), 4-methoxy-2,3,5-trimethylphenol (**13**) (1.33 g, 8.0 mmol), and triphenylphosphine (3.40 g, 13 mmol) in toluene (20 mL) was heated to 100 °C. Diisopropyl azodicarboxylate (DIAD; 3.40 g, 17 mmol) in toluene (10 mL) was added by a syringe pump over 2 h. The reaction mixture was stirred for an additional 2 h at 100 °C. After evaporation of the toluene, the residual brown viscous oil was partitioned between hexane and 85 % (v/v) aqueous methanol. The methanol phase was re-extracted with hexane and the combined hexane phases were concentrated in vacuo. The residual oil was purified by chromatography (silica gel, *n*-hexane/EtOAc 25:1) to yield **16** (1.208 g, 64 %) as a colorless viscous oil. $[\alpha]_D^{20}=+12.2$ ($c=1$ in $CHCl_3$); 94 % *de*; HPLC [Chiralcel OD-H column (*n*-heptane/2-propanol 99.6:0.4), UV 220 nm; 0.8 mL min^{-1}]: major diastereomer $t_R=7.7$ min ((*R*,*R*,*R*)-**16**), minor diastereomer $t_R=8.3$ min ((*S*,*R*,*R*)-**16**); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=6.32$ (s, 1H), 3.79 (s, 3H), 3.63 (s, 3H), 2.18 (s, 3H), 2.16 (s, 3H), 2.11 (s, 3H), 1.89–1.93 (m, 2H), 1.0–1.57 (m, 19H), 1.42 (s, 3H), 0.83–0.88 ppm (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=175.62$, 152.01, 149.48, 131.01, 127.80, 127.57, 117.5, 82.22, 60.43, 52.66, 40.96, 39.77, 37.84, 37.76, 37.70, 37.44, 33.21, 32.93, 28.39, 25.21, 24.84, 23.13, 23.04, 21.38, 20.15, 19.97, 17.72, 13.22, 13.19 ppm; IR (neat): $\tilde{\nu}=1736$ cm^{-1}; ESI-MS: *m/z*: 499.6 $[M+Na]^+$, 976.1 $[2M+Na]^+$; EI-MS: *m/z* (%): 476.4 (9), 166.2 (100); elemental analysis calcd (%) for $C_{30}H_{52}O_4$ (476.74): C 75.58, H 10.99; found: C 75.65, H 10.96.

(2*R*,6*R*,10*R*)-2-(4-Methoxy-2,3,5-trimethylphenoxy)-2,6,10,14-tetramethyl-1-pentadecanol (26): A solution of α-phenoxy ester **16** (487 mg, 1.02 mmol) in THF (6 mL) was added over 5 min to a suspension of $LiAlH_4$ (62 mg, 1.6 mmol) in THF (6 mL) at 0 °C. The reaction mixture was stirred at RT for 20 min and then quenched by the dropwise addition of water (75 μL) in THF (2 mL), followed by 2 N aq NaOH (160 μL) and water (80 μL). After stirring for 30 min, the mixture was filtered and the filtrate was concentrated in vacuo to provide **26** (458 mg, 100 %) as a colorless viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=6.64$ (s, 1H), 3.66 (s, 3H), 3.65 (s, 2H), 2.23 (s, 3H), 2.18 (s, 3H), 2.13 (s, 3H), 2.11 (br s, 1H), 1.47–1.80 (m, 3H), 1.0–1.45 (m, 18H), 1.15 (s, 3H), 0.83–0.88 ppm (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=152.91$, 149.12, 130.97, 129.83, 128.15, 122.45, 83.61, 68.42, 60.42, 39.77, 38.05, 37.84, 37.78, 37.69, 33.20, 33.17, 28.39, 25.21, 24.90, 23.13, 2304, 22.14, 21.01, 20.15, 20.08, 16.61, 14.16, 13.30 ppm; IR (neat): $\tilde{\nu}=3400$ cm^{-1}; ESI-MS: *m/z*: 471.6 $[M+Na]^+$.

(2*R*,6*R*,10*R*)-2-(4-Methoxy-2,3,5-trimethylphenoxy)-2,6,10,14-tetramethylpentadecanal (27): Alcohol **26** (450 mg, 1.0 mmol) was dissolved in dichloromethane (10 mL). The Dess–Martin periodinane reagent (600 mg, 1.4 mmol) was added and the reaction mixture was stirred at room temperature for 90 min. It was diluted with Et_2O (25 mL), and then saturated aq $NaHCO_3$ (12 mL) and $Na_2S_2O_3$ (1.9 g) were added and the heterogenous mixture was stirred at RT for 20 min. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated. The pale yellow oil was purified by chromatography (silica gel, *n*-hexane/EtOAc 20:1) to yield **27** (411 mg, 92 %) as a colorless viscous oil. $[\alpha]_D^{20}=+42.9$ ($c=1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=9.87$ (s, 1H), 6.33 (s, 1H), 3.64 (s, 3H), 2.18 (s, 6H), 2.15 (s, 3H), 1.65–1.87 (m, 2H), 1.0–1.57 (m, 19H), 1.31 (s, 3H), 0.83–0.88 ppm (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=205.25$, 152.31, 149.67, 131.45, 128.23, 127.54, 117.62, 85.91, 60.46, 39.78, 37.82, 37.73, 37.69, 37.65, 33.20, 32.98, 28.39, 25.21, 24.84, 23.13, 23.04, 20.82, 20.15, 19.99, 18.48, 16.61, 13.33, 13.22 ppm; IR (neat): $\tilde{\nu}=1735$ cm^{-1}; EI-MS: *m/z* (%): 446.4 $[M]^+$ (13), 166.3 (100); elemental analysis calcd (%) for $C_{30}H_{52}O_4$ (446.71): C 77.97, H 11.28; found: C 78.23, H 10.15.

(3*R*,7*R*,11*R*)-3-(4-Methoxy-2,3,5-trimethylphenoxy)-3,7,11,15-tetramethyl-1-hexadecene (28): Methyltriphenylphosphonium bromide (452 mg, 1.27 mmol) was suspended in THF (10 mL) and the mixture was cooled to 0 °C. A 1.6 M solution of *n*-butyllithium in hexane (0.75 mL, 1.20 mmol) was added dropwise to the mixture over 3 min, and the yellow mixture was stirred at 0 °C for 15 min. Then a solution of aldehyde **27** (401 mg, 0.90 mmol) in THF (4 mL) was added over 5 min and the yellow solution was stirred without a cooling bath for 15 min. The reaction mixture was partitioned between hexane and 85% (v/v) aqueous methanol and the aq methanol phase was re-extracted with hexane. The combined hexane phases were concentrated in vacuo and the product was purified by chromatography (silica gel, *n*-hexane/Et_2O 25:1) to afford **28** (375 mg, 94%) as a colorless viscous oil. $[\alpha]_D^{20}=+1.2$ ($c=1$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta=6.70$ (s,1 H), 6.06 (dd, $J=18$, 11 Hz, 1 H), 5.14 (d, $J=17$ Hz, 1 H), 5.14 (d, $J=12$ Hz, 1 H), 3.64 (s, 3 H), 2.18 (s, 3 H), 2.16 (s, 3 H), 2.11 (s, 3 H), 1.70 (t, $J=8.4$ Hz, 1 H), 1.0–1.57 (m, 19 H), 1.33 (s, 3 H), 0.83–0.87 ppm (m, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=151.80$, 150.39, 144.78, 130.52, 128.29, 127.35, 120.14, 114.00, 82.16, 60.43, 42.99, 39.78, 37.86, 37.83, 37.71, 33.21, 33.11, 28.39, 25.22, 24.87, 23.14, 23.04, 22.79, 21.67, 20.16, 20.11, 16.64, 13.66, 13.22 ppm; ESI-MS: *m/z*: 467.9 $[M+Na]^+$, 912.0 $[2M+Na]^+$; elemental analysis calcd (%) for $C_{30}H_{52}O_2$ (444.74): C 81.02, H 11.78; found: C 80.99, H 11.67

(3*R*,7*R*,11*R*)-3-(4-Methoxy-2,3,5-trimethylphenoxy)-3,7,11,15-tetramethyl-1-hexadecanol (29): A mixture of vinyl compound **28** (371 mg, 0.83 mmol) and tris(triphenylphosphine)rhodium(I) chloride (32.0 mg, 35 µmol) in THF (2.5 mL) was stirred at room temperature for 30 min. A 1 M solution of catecholborane in THF (1.8 mL, 1.8 mmol) was added to the orange solution. After stirring at room temperature for 4 h, the mixture was diluted with THF (6 mL) and treated with 2 N aq NaOH (4.0 mL) and 30% H_2O_2 (3.0 mL). The biphasic mixture was stirred for 1 h while the temperature was maintained at 25–35 °C. The mixture was extracted with TBME, and the organic phase was washed with brine, dried ($MgSO_4$), and concentrated on a rotary evaporator. The residual brown oil was purified by chromatography (silica gel, *n*-hexane/EtOAc 6:1) to afford **29** (353 mg, 91%) as a colorless viscous oil. $[\alpha]_D^{20}=-18.2$ ($c=1$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta=6.71$ (s, 1 H), 3.93 (q, $J=5.5$ Hz, 2 H), 3.65 (s, 3 H), 2.81 (t, $J=5.5$ Hz, 1 H, O-H), 2.23 (s, 3 H), 2.17 (s, 3 H), 2.12 (s, 3 H), 1.99 (t, $J=6$ Hz, 2 H), 1.47–1.82 (m, 3 H), 1.0–1.42 (m, 18 H), 1.24 (s, 3 H), 0.82–0.88 ppm (m, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=152.94$, 149.02, 130.92, 130.03, 127.97, 122.81, 85.01, 60.42, 60.18, 41.66, 40.31, 39.77, 37.99, 37.83, 37.81, 37.69, 33.20, 33.16, 28.39, 25.21, 24.87, 24.62, 23.13, 23.04, 22.52, 20.15, 20.08, 16.62, 14.41, 13.32 ppm; IR (neat): $\tilde{\nu}=3390\ cm^{-1}$; ESI-MS: *m/z*: 485.7 $[M+Na]^+$; elemental analysis calcd (%) for $C_{30}H_{54}O_3$ (462.75): C 77.87, H 11.76; found: C 77.99, H 11.61.

(*R*,*R*,*R*)-α-3,4-Dehydrotocopherol methyl ether (20): Alcohol **29** (112.2 mg, 0.24 mmol) was dissolved in dichloromethane (4 mL). The Dess–Martin periodinane reagent (123 mg, 0.29 mmol) was added and the solution was stirred at room temperature for 90 min. Trifluoroacetic acid (50 µL, 65 µmol) was added and the reaction mixture was stirred at room temperature for 2 h. It was diluted with Et_2O (15 mL); saturated aq $NaHCO_3$ (3 mL) and $Na_2S_2O_3$ (400 mg) were added and the mixture was stirred for 10 min. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated. The pale yellow oil was purified by chromatography (silica gel, *n*-hexane/EtOAc 40:1) to yield **20** (87.7 mg, 82%) as a colorless viscous oil. $[\alpha]_D^{20}=-38.2$ ($c=1$ in $CHCl_3$); 94% *de* (2*R*); HPLC [Chiralcel OD-H column (*n*-heptane/2-propanol 99.8:0.2), UV 220 nm; 0.8 mL min^{-1}]: major diastereomer $t_R=6.0$ min ((*R*,*R*,*R*)-**20**), minor diastereomer $t_R=7.2$ min ((*S*,*R*,*R*)-**20**); ^1H NMR (400 MHz, $CDCl_3$): $\delta=$ 6.50 (d, $J=10$ Hz, 1 H), 5.59 (d, $J=10$ Hz, 1 H), 3.62 (s, 3 H), 2.21 (s, 3 H), 2.18 (s, 3 H), 2.09 (s, 3 H), 1.0–1.7 (m, 21 H), 1.33 (s, 3 H), 0.82–0.89 ppm (m, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=150.52$, 147.27, 130.41, 129.89, 123.52, 123.02, 120.54, 118.27, 77.49, 60.75, 41.31, 39.78, 37.85, 37.75, 37.69, 33.21, 33.12, 28.39, 26.04, 25.22, 24.88, 23.14, 23.04, 21.79, 20.16, 20.06, 13.20, 11.97, 11.55 ppm; IR (neat): $\tilde{\nu}=1460$, 1406, 1377, 1263 cm^{-1}; EI-MS: *m/z* (%): 442.4 (4), 427 (5), 217 (100); elemental analysis calcd (%) for $C_{30}H_{50}O_2$ (442.72): C 81.39, H 11.38; found: C 81.31, H 11.18.

(*R*,*R*,*R*)-α-Tocopherol methyl ether (30): A mixture of dehydrotocopherol **20** (83.4 mg, 0.19 mmol) and 10% palladium on carbon (15 mg) in ethyl acetate (6 mL) was hydrogenated at room temperature and under 1 bar hydrogen for 30 min.[13] The mixture was filtered, the filtrate was concentrated, and the product was purified by chromatography (silica gel, hexane/EtOAc 40:1) to yield **30** (79.8 mg, 95%) as a colorless viscous oil. $[\alpha]_D^{20}=+0.3$ ($c=1$ in $CHCl_3$); 94% *de* (2*R*); HPLC [Chiralcel OD-H column (*n*-heptane:2-propanol 99.8:0.2), UV 220 nm, 0.8 mL min^{-1}]: major diastereomer $t_R=10.1$ min ((*R*,*R*,*R*)-**30**), minor diastereomer $t_R=$ 8.5 min ((*S*,*R*,*R*)-**30**); ^1H NMR (400 MHz, $CDCl_3$): $\delta=3.63$ (s,3 H), 2.58 (t, $J=7$ Hz, 2 H), 2.19 (s, 3 H), 2.14 (s, 3 H), 2.09 (s, 3 H), 1.72–1.86 (m, 2 H), 1.0–1.6 (m, 21 H), 1.24 (s, 3 H), 0.84–0.88 ppm (m, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=149.77$, 148.18, 128.14, 126.12, 123.29, 117.94, 75.20, 60.82, 40.47, 39.79, 37.87, 37.83, 37.70, 33.22, 33.12, 31.69, 28.40, 25.22, 24.86, 24.31, 23.14, 23.05, 21.45, 21.05, 20.17, 20.08, 12.96, 12.18, 12.10 ppm; IR (neat): $\tilde{\nu}=1456$, 1404, 1377, 1258 cm^{-1}; EI-MS: *m/z* (%): 444.4 (100); elemental analysis calcd (%) for $C_{30}H_{52}O_2$ (444.74): C 81.02, H 11.78; found: C 80.82, H 11.62.

2-(1,3-Dithian-2-yl)-4-methoxy-3,5,6-trimethylphenol (14): A mixture of 2-hydroxy-5-methoxy-3,4,6-trimethylbenzaldehyde (1.16 g, 6.0 mmol), 1,3-propanedithiol (713 mg, 6.6 mmol), and tetrabutylammonium tribromide (58 mg, 0.12 mmol) in THF (5 mL) was stirred at RT for 7 h. It was poured into water and extracted with Et_2O. The organic phase washed with brine, dried ($MgSO_4$), and concentrated on a rotary evaporator. The residual oil was purified by chromatography (silica gel, *n*-hexane/EtOAc 6:1) to yield **14** (1.70 g, 100%) as a pale yellow solid. The analytical sample was prepared by crystallization from Et_2O/hexane. White crystals; m.p. 93–96 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta=6.95$ (br s, 1 H), 5.64 (s, 1 H), 3.60 (s, 3 H), 3.01–3.10 (m, 2 H), 2.87–2.94 (m 2 H), 2.32 (s, 3 H), 2.18 (s, 3 H), 2.14 (s, 3 H), 2.15–2.23 (m, 1 H), 1.85–1.98 ppm (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=150.98$, 150.17, 132.06, 125.67, 124.17, 119.17, 60.89, 45.37, 32.11, 25.23, 13.32, 12.76, 12.51 ppm; ESI-MS (neg): 283 [M−H]; ESI-MS (pos.): 307 $[M+Na]^+$, 591 $[2M+Na]^+$; elemental analysis calcd (%) for $C_{14}H_{20}O_2S_2$ (284.43): C 59.12, H 7.09; found: C 59.19, H 6.98.

(2*R*,6*R*,10*R*)-2-[2-(1,3-Dithian-2-yl)-4-methoxy-3,5,6-trimethylphenoxy]-2,6,10,14-tetramethylpentadecanoic acid methyl ester (17): Diisopropyl azodicarboxylate (DIAD, 290 mg, 1.43 mmol) was added to a solution of **2** (344 mg, 1.04 mmol), **14** (356 mg, 1.25 mmol), and triphenylphosphine (330 mg, 1.26 mmol) in toluene (8 mL). The yellow solution was stirred at 25 °C for 20 h. Additional amounts of triphenylphosphine (165 mg and 105 mg) and DIAD (145 mg and 91 mg) were added after 4 h and 8 h of stirring. The reaction mixture was partitioned between hexane and 85% (v/v) aqueous methanol. The methanol phase was re-extracted with hexane and the combined hexane phases were concentrated in vacuo. The residual oil was purified by chromatography (silica gel, *n*-hexane/EtOAc 25:1) to yield **17** (424.5 mg, 68%) as a colorless viscous oil. $[\alpha]_D^{20}=+8.6$ ($c=1$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta=6.06$ (s, 1 H), 3.83 (s, 3 H), 3.64 (s, 3 H), 2.95–3.05 (m, 2 H), 2.77–2.87 (m, 2 H), 2.65 (s, 3 H), 2.1–2.3 (m, 2 H), 2.13 (s, 3 H), 2.02 (s, 3 H), 1.84–1.97 (m, 2 H), 1.0–1.57 (m, 19 H), 1.16 (s, 3 H), 0.83–0.88 ppm (m, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=174.59$, 154.47, 147.59, 130.96, 130.73, 130.32, 85.05, 60.21, 52.58, 46.93, 42.37, 39.77, 37.84, 37.77, 37.72, 37.70, 33.23, 33.15, 32.93, 32.76, 28.39, 26.08, 25.21, 24.94, 23.13, 23.03, 22.49, 20.66, 20.15, 14.94, 14.51, 13.53 ppm; IR (neat): $\tilde{\nu}=1739\ cm^{-1}$; ESI-MS: *m/z*: 617.3 $[M+Na]^+$, 1211.2 $[2M+Na]^+$; elemental analysis calcd (%) for $C_{34}H_{58}O_4S_2$ (594.95): C 68.64, H 9.83; found: C 68.63, H 9.68.

(2*R*,6*R*,10*R*)-2-[2-(1,3-Dithian-2-yl)-4-methoxy-3,5,6-trimethylphenoxy]-2,6,10,14-tetramethyl-1-pentadecanol (31): $LiAlH_4$ (76 mg, 2.0 mmol) was added to a solution of α-phenoxy ester **17** (424 mg, 0.71 mmol) in THF (12 mL) at 0 °C and the mixture was stirred at room temperature for 40 min. Excess hydride was quenched with sodium sulfate decahydrate; after stirring for 20 min, the mixture was filtered and the filtrate was concentrated in vacuo to give **31** (409 mg, 101%) as a colorless gum. ^1H NMR (400 MHz, $CDCl_3$): $\delta=5.96$ (s, 1 H), 3.81 (dd, $J=11$, 5 Hz, 1 H), 3.74 (dd, $J=11$, 7 Hz, 1 H), 3.64 (s, 3 H), 2.98–3.10 (m, 2 H), 2.82–2.90 (m, 2H), 2.67 (s, 3H), 2.26 (brs, 1H), 2.16 (s, 3H), 2.15 (s, 3H), 1.65–2.0 (m, 3H), 1.0–1.55 (m, 19H), 1.16 (s, 3H), 0.82–0.87 ppm (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=154.15$, 147.60, 131.04, 131.02, 130.98, 130.31, 86.39, 68.72, 60.23, 47.42, 39.78, 38.20, 37.84, 37.69, 33.21, 33.04, 32.99, 30.72, 28.39, 26.00, 25.21, 24.94, 23.14, 23.04, 22.91, 21.21, 20.16, 20.10, 16.62, 14.52, 13.65 ppm; IR (neat): $\tilde{\nu}=3440\,cm^{-1}$; ESI-MS: *m/z*: 589.3 $[M+Na]^+$.

(2*R*,6*R*,10*R*)-2-[2-(1,3-Dithian-2-yl)-4-methoxy-3,5,6-trimethylphenoxy]-2,6,10,14-tetramethylpentadecan-1-yl benzenesulfonate (32): Benzenesulfonyl chloride (826 mg, 4.7 mmol) was added to a solution of alcohol **31** (409 mg, 0.71 mmol) in pyridine (4 mL), and the mixture was stirred at room temperature for 6 h. It was quenched with ice water and partitioned between TBME and 2 N aq HCl. The organic phase was washed with brine containing a small amount of $NaHCO_3$, dried ($MgSO_4$), and concentrated on a rotary evaporator. The residual colorless oil was purified by chromatography (silica gel, hexane/EtOAc 12:1) to yield **32** (430 mg, 84%) as a colorless viscous oil. $[\alpha]_D^{20}=-2.2$ ($c=1$ $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.52$–7.92 (m, 5H), 5.79 (s, 1H), 4.31 (brd, $J=9$ Hz, 1H), 4.23 (brd, $J=10$ Hz, 1H), 3.62 (s, 3H), 2.95–3.03 (m, 2H), 2.75–2.83 (m, 2H), 2.64 (s, 3H), 2.11 (s, 3H), 2.04 (s, 3H), 1.65–1.95 (m, 3H), 1.0–1.55 (m, 19H), 1.09 (s, 3H), 0.81–0.88 ppm (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=154.33$, 147.24, 136.28, 134.23, 130.98, 130.90, 130.82, 130.31, 129.65, 128.34, 83.30, 73.46, 60.18, 46.97, 39.79, 38.26, 37.97, 37.86, 37.83, 37.71, 33.25, 32.76, 28.39, 25.89, 25.22, 24.95, 23.14, 23.04, 21.85, 20.16, 20.10, 16.48, 14.56, 13.58 ppm; IR (neat): $\tilde{\nu}=1448$, 1363, 1187 cm^{-1}; ESI-MS: *m/z*: 729.3 $[M+Na]^+$; elemental analysis calcd (%) for $C_{39}H_{62}O_5S_3$ (707.09): C 66.25, H 8.84, found: C 66.18, H 8.70.

(2*R*,6*R*,10*R*)-2-[2-(1,1,3,3-Tetraoxido-1,3-dithian-2-yl)-4-methoxy-3,5,6-trimethylphenoxy]-2,6,10,14-tetramethylpentadecan-1-yl benzenesulfonate (33): A solution of benzenesulfonate **32** (411 mg, 0.58 mmol) in dichloromethane (25 mL) was treated with 70% 3-chloroperbenzoic acid reagent (*m*CPBA; 1.20 g, 4.9 mmol) at room temperature for 4 h. The reaction mixture was quenched with cold aqueous $NaHSO_3$ and the product was extracted with TBME. The organic phase was washed with sat. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated on a rotary evaporator. The residual oil was purified by chromatography (silica gel, *n*-hexane/CH_2Cl_2/EtOAc 4:2:1) to provide **33** (421 mg, 94%) as a colorless glass. $[\alpha]_D^{20}=-5.2$ ($c=1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.58$–7.99 (m, 5H), 6.59 (s, 1H), 4.38 (d, $J=11$ Hz, 1H), 4.23 (d, $J=11$ Hz, 1H), 3.66 (s, 3H), 3.57–3.74 (m, 2H), 3.41–3.50 (m, 2H), 2.72–2.86 (m, 1H), 2.68 (s, 3H), 2.52–2.62 (m, 1H), 2.19 (s, 3H), 2.11 (s, 3H), 0.8–1.8 (m, 21H), 1.07 (s, 3H), 0.83–0.88 (m, 9H), 0.74 ppm (d, $J=6.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=154.68$, 151.84, 135.68, 134.80, 134.77, 133.21, 131.21, 129.95, 128.43, 114.73, 84.82, 81.99, 74.70, 60.27, 54.13, 54.06, 39.78, 37.84, 37.77, 37.70, 37.39, 33.22, 33.11, 28.39, 25.21, 24.92, 23.13, 23.04, 22.81, 20.95, 20.15, 19.88, 18.56, 18.05, 16.59, 14.03 ppm; IR (neat): $\tilde{\nu}=1448$, 1337, 1131 cm^{-1}; ESI-MS: *m/z*: 793.2 $[M+Na]^+$, 1562.9 $[2M+Na]^+$; elemental analysis calcd (%) for $C_{39}H_{62}O_9S_3$ (771.09): C 60.75, H 8.10; found: C 60.79, H 7.94.

Spiro compound 34: A 1 M solution of sodium methoxide in methanol (10 mL) was added to a solution of benzenesulfonate **33** (401 mg, 0.52 mmol) in THF (3 mL). The mixture was stirred at room temperature for 30 min and then partitioned between TBME and water. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated on a rotary evaporator. The residual brown oil was purified by chromatography (silica gel, *n*-hexane/CH_2Cl_2/EtOAc 4:2:1) to afford **34** (312 mg, 98%) as a colorless viscous oil. $[\alpha]_D^{20}=-22.9$ ($c=1.2$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=4.06$–4.15 (m, 1H), 3.64 (s, 3H), 3.57–3.63 (m, 1H), 3.36–3.50 (m, 2H), 3.26 (d, $J=14$ Hz, 1H), 3.16 (d, $J=14$ Hz, 1H), 2.63 (s, 3H), 2.40–2.50 (m,2H), 2.22 (s, 3H), 2.09 (s, 3H), 1.0–1.8 (m, 21H), 1.28 (s, 3H), 0.83–0.88 ppm (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=152.26$, 152.12, 134.93, 131.97, 126.13, 105.88, 95.36, 73.83, 60.21, 47.90, 45.99, 41.01, 40.51, 39.78, 37.87, 37.74, 37.71, 37.57, 33.23, 33.03, 28.39, 25.22, 24.83, 23.14, 23.04, 22.60, 21.22, 20.16, 20.06, 19.22, 16.64, 13.70, 13.11 ppm; IR (neat): $\tilde{\nu}=1460$, 1383, 1316, 1122 cm^{-1}; ESI-MS: *m/z*: 635.2 $[M+Na]^+$, 1247.0 $[2M+Na]^+$; elemental analysis calcd (%) for $C_{33}H_{56}O_6S_2$ (612.92): C 64.67, H 9.21; found: C 64.57, H 9.04.

(*R*,*R*,*R*)-α-Tocopherol methyl ether (30): A solution of spiro compound **34** (108.3 mg, 0.18 mmol) in dry THF (4 mL) was cooled to −78 °C. A 0.2 M solution of freshly prepared lithium naphthalenide in THF (4 mL, 0.8 mmol) was added by syringe over 1 min, and the mixture was stirred at −78 °C for 4 min. Methanol (40 µL, 32 mg, 1 mmol) was added followed by a second portion of the 0.2 M lithium naphthalenide solution (5 mL, 1 mmol). After stirring at −78 °C for 5 min, the mixture was quenched with methanol, partitioned between TBME and brine, dried ($MgSO_4$), and concentrated on a rotary evaporator. The residue was purified by chromatography (silica gel, hexane/EtOAc 50:1, *n*-hexane/CH_2Cl_2 3:1) to give **30** (67.3 mg, 86%) as a colorless viscous oil. $[\alpha]_D^{20}=+0.4$ ($c=1$ in $CHCl_3$); 94% *de* (2*R*); HPLC [Chiralcel OD-H column (*n*-heptane/2-propanol 99.8:0.2), UV 220 nm, 0.8 $mL\,min^{-1}$]: major diastereomer $t_R=9.1$ min ((*R*,*R*,*R*)-**30**), minor diastereomer $t_R=7.7$ min ((*S*,*R*,*R*)-**30**); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=3.63$ (s, 3H), 2.58 (t, $J=7$ Hz, 2H), 2.19 (s, 3H), 2.14 (s, 3H), 2.09 (s, 3H), 1.72–1.87 (m, 2H), 1.0–1.6 (m, 21H), 1.24 (s, 3H), 0.84–0.88 ppm (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=149.78$, 148.18, 128.14, 126.11, 123.30, 117.94, 75.20, 60.80, 40.48, 39.79, 37.87, 37.83, 37.70, 33.21, 33.12, 31.70, 28.40, 25.22, 24.86, 24.31, 23.14, 23.04, 21.45, 21.05, 20.16, 20.08, 12.96, 12.17, 12.09 ppm; IR (neat): $\tilde{\nu}=1456$, 1257, 1090 cm^1; EI-MS: *m/z* (%): 444.4 (100); elemental analysis calcd (%) for $C_{30}H_{52}O_2$ (444.74): C 81.02, H 11.78, found: C 81.22, H 11.79.

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