



Supporting Information

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Reagent Directing Group Controlled Organic Synthesis:

Total Synthesis of (*R,R,R*)- α -Tocopherol

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Supplementary Material

(18 pages)

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I General

All reactions were carried out in dried glassware under an Argon atmosphere (Argon 5.0 from Messer-Griesheim). All reagents were obtained commercially unless otherwise noted. All solvents were dried and distilled by standard procedures. Chromatographic purification of products was accomplished using flash chromatography on Macherey-Nagel silica gel 60 (230-400 mesh) unless otherwise noted. Room temperature (RT) refers to 20-22 °C.

Nuclear magnetic resonance spectra were acquired on a Varian Mercury spectrometer (300 MHz, 121.5 MHz and 75.5 MHz for ^1H , ^{31}P and ^{13}C respectively), a Bruker AC-250 (250 MHz for ^1H -NMR), a Bruker Avance 400 (400 MHz and 100.6 MHz for ^1H and ^{13}C respectively) and a Bruker Avance 500 (500 MHz and 125 MHz for ^1H and ^{13}C respectively) and are referenced internally according to residual protio solvent signals (CDCl_3 : 7.26 ppm (^1H), 77.10 ppm (^{13}C)). Data for ^1H -NMR are recorded as follows: chemical shift (δ in ppm), multiplicity (s, singlet; br, broad signal; d, doublet; t, triplet; q, quartet; quint, quintet; hept, m, multiplet; m_c, symmetrical multiplet), integration, coupling constant (Hz). Data for ^{13}C -NMR are reported in terms of chemical shift (δ in ppm), integration, coupling constant (Hz). Chemical ionization mass spectra were obtained with an MS9 instrument (AEI, Manchester,

GB), with ionization energy 70 eV and 250 °C temp. of ion source. High-resolution mass spectra were obtained on a Finnigan MAT 8200 instrument. The enantiomeric excess (*ee*) of the products was determined by HPLC using Daicel Chiralpak AD, AD-H and Chiracel OD-H columns. Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

Hydroformylation experiments were performed in stainless steel tube autoclaves with synthesis gas (CO 3.7, H₂ 4.3, 1:1, Messer-Griessheim).

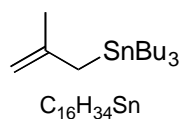
Caution: All operations involving carbon monoxide must be carried out in a well-ventilated fume hood. Use of a gas-leak detector for carbon monoxide is highly recommended.

List of abbreviations:

Bn	benzyl	Cy	cyclohexane
DIBAL-H	diisobutylaluminium hydride	DMAP	<i>para</i> -dimethylaminopyridine
<i>o</i> -DPPB	<i>ortho</i> -diphenylphosphanyl benzoate	DCC	<i>N,N'</i> -dicyclohexyl carbodiimide
PE	petroleum ether (bp. 40-65°C)	TBME	<i>tert</i> -butyl methyl ether
TBAF	tetra- <i>n</i> -butylammonium fluoride		

II Experimental procedures and characterizations

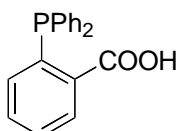
Tributyl-(2-methylallyl)-stannane



Mol. Wt.: 345.15

The stannane was prepared according to a literature procedure.^[1]

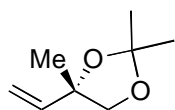
ortho-diphenylphosphanylbenzoic acid (*o*-DPPBA)



Mol. Wt.: 306.29

The *o*-DPPBA was prepared according to a literature procedure.^[2]

(S)-2,2,4-Trimethyl-4-vinyl-1,3-dioxolane (3)



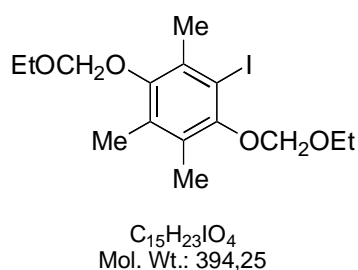
$C_8H_{14}O_2$
Mol. Wt.: 142,20

a) Swern oxidation: To a stirred solution of oxalyl chloride (9.5 ml, 110 mmol, 1.1 eq.) in CH_2Cl_2 (500 ml) was added dropwise during 5 min under argon at $-60^\circ C$ a solution of DMSO (15.6 ml, 220 mmol, 2.2 eq.) in CH_2Cl_2 (100 ml). After 10 min further stirring the solution of (S)-2,2,4-trimethyl-1,3-dioxolane-4-methanol (2), obtained by enzymatic hydrolysis^[3] (14.62 g, 100 mmol; *ee* 99.3%, GC on permethylated β -cyclodextrine of benzoate derivative) in CH_2Cl_2 (50 ml) was dropped in during 5 min. After further 5 min stirring NEt_3 (69.7 ml, 500 mmol, 5.0 eq.) was added, and the mixture warmed up to $0^\circ C$. Water (150 ml) was added, and the lower phase of the two-phase mixture was washed successively with H_2O (1 \times 150 ml) and brine (2 \times 150 ml). The aqueous solutions were extracted with CH_2Cl_2 (150 ml). The combined organic extracts were dried over $MgSO_4$ and evaporated at $0-5^\circ C$ and a vacuum of 18 mbar. The crude residue (14.3 g) was distilled bulb-to-bulb in a Kugelrohrföfen at 18 mbar and $100^\circ C$ to give the aldehyde^[4] as a colourless oil (10.72 g, GC purity 95.6%, containing 2.9% NEt_3 , 71.1 mmol, 71%). The crude yield of the reaction was estimated by GC area% to >90%; loss of material is due to the low boiling point of the product. Analytical data for the title compound: ^1H-NMR (250 MHz, $CDCl_3$): δ = 1.35, 1.45, 1.46 (3 \times s, 3 CH_3), 3.48 (d, 1H, J = 9.0 Hz), 4.26 (d, 1H, J = 9.0 Hz), 9.66 (CHO); **IR** (film): ν = 3439 (s), 2988 (s), 1737 (s), 1456 (m), 1376 (s), 1260 (s), 1213 (s), 1118 (s), 1061 (s), 848 cm^{-1} (m); **MS** (70 eV): m/z (%) = 129 ($[M-CH_3]^+$, 19), 115 ($[M-CHO]^+$, 63), 59 ($[C_3H_7O]^+$, 34), 57 (86), 43 ($[CHO]^+$, 100); **CHN** calcd. C: 58.32, H: 8.39, found C: 57.50, H: 8.37, N: 0.35 (due to impurity NEt_3); $[\alpha]_D^{20} = +23.5^\circ$ ($c = 1$ in $CHCl_3$).

b) Wittig reaction^[5]: To a stirred suspension of methyltriphenylphosphonium bromide (21.43 g, 60.0 mmol, 1.2 eq.) in THF (400 ml) *n*-BuLi (34.37 ml, 55.0 mmol, 1.6 M in *n*-hexane) was dropped in at room temperature to form a yellow suspension. After 30 min stirring, the aldehyde (7.20 g, 50.0 mmol) was added, and the mixture stirred for another 2 h. $NaHCO_3$ (8.4 g, 100.0 mmol) and pentane (100 ml) were added, and the mixture filtered through a pad of Speedex. The yellow filtrate was evaporated at the rotary evaporator ($0-10^\circ C$ bath temperature/ 50 mbar) to give a yellow residue (26.82 g) which was distilled bulb-to-bulb in a Kugelrohrföfen at $50 \rightarrow 18$ mbar/ $50^\circ C$, then up to $130^\circ C$, giving a liquid (7.09 g, GC content 55%, crude yield at this stage 55%), which was distilled bulb-to-bulb a second time (room temperature to $30^\circ C$ / $50 \rightarrow 22$ mbar) to yield olefin 3 as a colourless liquid (2.58 g, 17.6 mmol, 35%, GC purity 96.6%). The crude yield of the reaction was estimated by GC area% to >90%; the yield of product with GC contents ranging from 9 to 55% during

distillation was determined to 89→55%; loss of material is due to the low boiling point of the product. Analytical data for the title compound: ¹H-NMR (250 MHz, CDCl₃): δ = 1.38 (s, 3H), 1.41 (s, 3H), 1.45 (s, 3H), 3.79 (AB, 1H, *J* = 8.4 Hz), 3.87 (AB, 1H, *J* = 8.3 Hz), 5.10 (dd, 1H, *J* = 10.7, 1.3 Hz), 5.31 (dd, 1H, *J* = 17.3, 1.3 Hz), 5.94 (dd, 1H, *J* = 17.3, 10.7 Hz); IR (film): ν = 3092 (w), 2985 (s), 2869 (m), 1456 (w), 1373 (s), 1254 (m), 1209 (s), 1113 (m), 1061 (s), 988 (m), 924 (m), 858 cm⁻¹ (m); MS (70 eV): *m/z* (%) = 129 ([M-CH₃]⁺, 22), 72 ([C₄H₈O]⁺, 23), 43 ([CHO]⁺, 100); CHN calcd. C: 67.57, H: 9.92, found C: 67.37, H: 10.07; [α]_D²⁰ = +10.9° (c = 1.00 in CHCl₃); [α]₃₆₅²⁰ = +44.0° (c = 1.00 in CHCl₃).

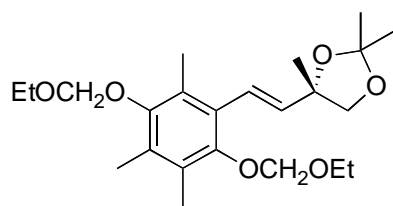
2-Iodo-3,5,6-trimethylhydroquinone-1,4 bis(ethoxymethyl) ether (4)



For the synthesis of compound **4**, 2-iodo-3,5,6-trimethylhydroquinone-1,4 was prepared according to literature procedures^[6] from 2,3,5-trimethylphenol by oxidative iodination to 2-iodo-3,5,6-trimethyl-p-benzoquinone (yield 57-64% on 0.1-0.5 mol scale), followed by dithionite reduction (95-98%). A solution of this iodo-hydroquinone (37.4 g, 134 mmol), (±)camphor-10-sulfonic acid (1.4 g, 6.0 mmol, 4.5 mol%), and formaldehyde diethylacetal (252 ml, 2.01 mol, 15 eq.) was refluxed for 8 d using a Soxhlet extractor containing 300 g of 4Å molecular sieve. After cooling to room temperature the brown solution was washed with NaOH (3×200 ml, 2N) and brine (200 ml). The aqueous layer was extracted with hexane (200 ml), and the combined organic extracts were dried over MgSO₄, filtered and evaporated under reduced pressure. The crude yellow solid (50.68 g) was recrystallized under argon from ca. 65 ml MeOH/ water (95:5): **4** as slightly yellowish crystals (44.39 g, 113.0 mmol, 84%, GC purity 99.5%). Analytical data for the title compound: ¹H-NMR (250 MHz, CDCl₃): δ = 1.27 (t, 3H, *J* = 7.0 Hz), 1.29 (t, 3H, *J* = 7.1 Hz), 2.18 (s, 3H), 2.26 (s, 3H), 2.44 (s, 3H), 3.85 (q, 2H, *J* = 7.0 Hz), 3.94 (q, 2H, *J* = 7.1 Hz), 4.92 (s, 2H), 5.02 (s, 2H); MS (70 eV): *m/z* (%) = 394 (M⁺, 2.5), 277 ([M -2×C₃H₇O +H]⁺, 3), 207 ([M -C₃H₇O -HI]⁺, 4.5), 163 ([M -C₃H₇O -C₂H₅O -I]⁺, 1.5), 149 ([M -2×C₃H₇O -HI]⁺, 0.5), 59 ([C₃H₇O]⁺, 100); CHN calcd. C: 45.70, H: 5.88, I: 32.19, found C: 45.58, H: 5.67, I: 32.19.

(S)-3,5,6-Trimethyl-2-(2,2,4-trimethyl-1,3-dioxolane-4-*E*-ethenyl)-1,4-benzenediol

bis(ethoxymethyl) ether (**5**)

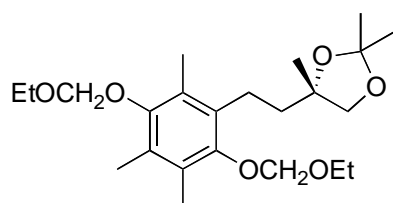


C₂₃H₃₆O₆
Mol. Wt.: 408,53

A mixture of dioxolane **3** (2.22 g, 15.6 mmol, 1.3 eq.), ether **4** (4.73 g, 12.0 mmol), Pd(OAc)₂ (134 mg, 0.6 mmol, 5 mol%), tetrabutylammonium bromide (3.87 g, 12.0 mmol), and NaHCO₃ (5.04 g, 60.0 mmol) in DMF (80 ml) was stirred under argon for 2 d at 110°C bath temperature. GC and TLC control (SiO₂, EtOAc/ hexane 1:3, R_f (**4**) = 0.50, R_f (**5**) = 0.37) showed already almost complete turnover after 16 h. After cooling most of the DMF was evaporated at 50°C/ 1 mbar. The remainder was taken up in EtOAc, filtered over Speedex, and evaporated to dryness in vacuo. The crude residue was chromatographed (300 g SiO₂, 0.04-0.063 mm, EtOAc/ hexane 1:9) to yield **5** as a yellowish oil (3.69 g, 9.0 mmol, 75%, GC purity 99.5%). Analytical data for the title compound: ¹H-NMR (250 MHz, CDCl₃): δ = 1.24 (t, 3H, *J* = 7.1 Hz), 1.27 (t, 3H, *J* = 7.1 Hz), 1.46 (s, 3H), 1.47 (s, 3H), 1.48 (s, 3H), 2.20 (s, 6H), 2.24 (s, 3H), 3.75-4.00 (m, 6H), 4.87 (s, 2H), 4.92 (s, 2H), 6.07 (d, 1H, *J* = 16.3 Hz), 6.63 (d, 1H, *J* = 16.3 Hz); IR (film): ν = 2978 (s), 2932 (m), 2872 (m), 1454 (s), 1387 (s), 1242 (s), 1213 (m), 1180 (s), 1160 (s), 1113 (m), 1057 (s), 975 (s), 849 cm⁻¹ (w); MS (70 eV): *m/z* (%) = 350 ([M - C₃H₇O + H]⁺, 0.6), 347 ([M - EtOH - CH₃]⁺, 2.5), 291 ([M - 2×C₃H₇O + H]⁺ or [M - C₆H₁₁O₂ - 2H]⁺, 4), 261 ([M - 2×C₃H₇O - 2CH₃ + H]⁺, 70), 115 ([C₆H₁₁O₂]⁺, 16), 59 ([C₃H₇O]⁺, 100); CHN calcd. C: 67.62, H: 8.88, found C: 67.35, H: 8.88; [α]_D²⁰ = +0.8° (c = 1.00 in CHCl₃); [α]_D²⁰ = +9.4° (c = 1.00 in CHCl₃).

(S)-3,5,6-Trimethyl-2-(2,2,4-trimethyl-1,3-dioxolane-4-ethyl)-1,4-benzenediol

bis(ethoxymethyl) ether (**6**)

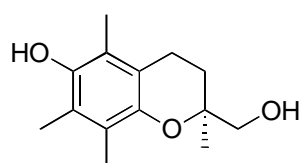


C₂₃H₃₈O₆
Mol. Wt.: 410,54

To the solution of olefin **5** (3.26 g, 8.00 mmol) in MeOH (125 ml) NaOAc (0.74 g, 9.00 mmol) and 5% Pd/C (0.85 g) were added. The mixture was stirred at room temperature under an atmosphere of hydrogen at ambient pressure for 2 h (measured hydrogen uptake 217 ml), filtered through a pad of Speedex, evaporated to dryness, taken up in a small amount of EtOAc, filtered a second time through Speedex, and evaporated to dryness in vacuo. The crude residue (3.11 g) was chromatographed (200 g SiO₂, EtOAc/ hexane 1:9) to yield **6** as a colorless oil (3.06 g, 7.40 mmol, 93%, GC purity 99.5%). Analytical data for the title compound: ¹H-NMR (250 MHz, CDCl₃): δ = 1.271 (t, 3H, *J* = 7.1 Hz), 1.275 (t, 3H, *J* =

7.1 Hz), 1.38 (s, 3H), 1.43 (s, 6H), 1.69 (m_c, 2H), 2.18 (s, 6H), 2.24 (s, 3H), 2.73 (m_c, 2H), 3.75-3.92 (m, 6H), 4.89-4.96 (m, 4H); **IR** (film): ν = 2978 (s), 2932 (m), 2873 (m), 1457 (s), 1373 (s), 1243 (s), 1212 (w), 1178 (m), 1160 (m), 1116 (m), 1056 (s), 975 cm⁻¹ (s); **MS** (70 eV): m/z (%) = 352 ([M- C₃H₇O +H]⁺, 2), 293 ([M -2×C₃H₇O +H]⁺, 0.5), 291 (1), 276 (1.5), 217 (8), 177 (3), 115 ([C₆H₁₁O₂]⁺, 4), 59 ([C₃H₇O]⁺, 100); **CHN** calcd. C: 67.29, H: 9.33, found C: 67.09, H: 9.48; $[\alpha]_D^{20} = +1.86^\circ$ (c = 0.7 in CHCl₃); $[\alpha]_{365}^{20} = +8.3^\circ$ (c = 0.7 in CHCl₃).

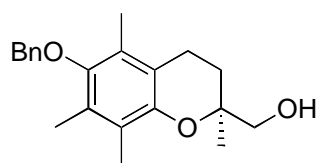
(S)-3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-benzopyran-2-methanol (**7**)



C₁₄H₂₀O₃
Mol. Wt.: 236,31

To the stirred solution of ether **6** (2.87 g, 7.00 mmol) in EtOH (35 ml) was added at room temperature aqueous conc. HCl (7 ml). The yellowish solution became darker after 6 h and turned red after 20 h. TLC control (SiO₂, EtOAc/ hexane 1:3, R_f (**6**) = 0.30, R_f (**7**) = 0.09). After 30 h total (complete cyclization)^[7-10], the solution was poured on a saturated aqueous solution (0°C) of NaHCO₃, and extracted with diethyl ether. This extract was washed with brine, dried over MgSO₄ and evaporated to dryness in vacuo. The remaining yellow oil (1.88 g) was chromatographed (300 g SiO₂, 0.04-0.063 mm, EtOAc/ hexane 1:2) to yield **7** (1.49 g, 6.30 mmol, 90%). After treatment of this product with a mixture of *n*-hexane and diethyl ether and crystallization for 1 h at -20°C colourless crystals were obtained which were isolated by suction filtration and dried under vacuum to give pure **7** (1.43 g, 6.0 mmol, 86%, GC purity 99.8%). Analytical data for the title compound: **mp**: 128.5-129.5°C (lit.^[9]: 129.5-131.5°C); **¹H-NMR** (400.13 MHz, CDCl₃): δ = 1.23 (s, 3H), 1.70-1.76 (m, 1H), 1.97-2.04 (m, 1H), 2.12 (s, 3H), 2.13 (s, 3H), 2.17 (s, 3H), 2.65 – 2.69 (m, 2H), 3.60 (d, 1H, J = 11.2 Hz), 3.66 (d, 1H, J = 11.2 Hz), 4.25 (bs, 1H), (Ar-OH not detected); **¹³C-NMR** (100.62 MHz, CDCl₃): δ = 11.3, 11.8, 12.2, 20.3, 20.4, 27.9, 69.4, 75.1, 117.3, 118.8, 121.4, 122.5, 144.9, 145.1; **HPLC** (Chiracel OD, hexane/ EtOH (95:5): t_R (**7**) = 18.0 min, t_R (ent-**7**) = 14.8 min, ee = 99.5%; $[\alpha]_D^{20.5} = -2.1^\circ$ (c = 1.00, CHCl₃).

(S)-(6-Benzyloxy)-2,5,7,8-tetramethyl-3,4-dihydro-2-H-chromen-2-yl)methanol (**I**)

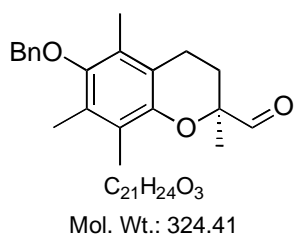


C₂₁H₂₆O₃
Mol. Wt.: 326.43

To a solution of alcohol **7** (418 mg, 1.77 mmol, 1 eq.) in DMF (4 ml) was added K₂CO₃ (1.77 g, 12.8 mmol, 7.23 eq.). Subsequently benzylchloride (0.52 ml, 571 mg, 4.51 mmol, 2.55 eq.) was added and stirred for 20 h. The reaction mixture was poured into water (25 ml) and the aqueous layer was extracted

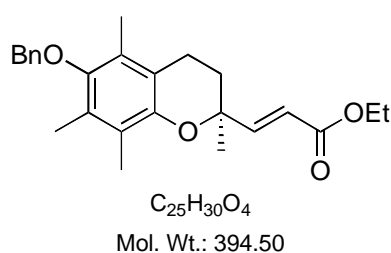
twice with TBME (20 ml). After removal of the solvents in vacuo and drying over Na₂SO₄ the crude product was then purified by flash chromatography (Cy/CH₂Cl₂ 1:1→0:1) to furnish the title compound **I** (565 mg, 1.73 mmol, 98%) as a colorless, crystalline solid. Analytical data for the title compound: **mp**: 66-67 °C; **¹H-NMR** (400 MHz, CDCl₃): δ = 1.27 (s, 3H), 1.74-1.80 (m, 1H), 1.98-2.10 (m, 2H) 2.14 (s, 3H), 2.21 (s, 3H), 2.26 (s, 3H), 2.62-2.74 (m, 2H), 3.63 (d, 1H, *J* = 11.2 Hz), 3.68 (d, 1H, *J* = 11.2 Hz), 4.73 (s, 2H), 7.34-7.45 (m, 3H), 7.52-7.54 (m, 2H); **¹³C-NMR** (100 MHz, CDCl₃): δ = 11.9, 12.0, 12.9, 20.2, 20.6, 27.8, 69.4, 74.8, 75.4, 117.6, 122.9, 126.2, 127.7, 127.8 (2C), 128.3, 128.5 (2C), 137.9, 147.3, 148.7; [**α**]_D²⁰: -2.8° (c = 1.10 in CHCl₃).

(S)-6-(Benzyloxy)-2,5,7,8-tetramethyl-3,4-dihydro-2H-chromene-2-carbaldehyde (II)



To a solution of freshly distilled oxalyl chloride (0.95 ml, 1.38 g, 10.88 mmol, 1.18 eq.) in CH₂Cl₂ (20 ml) at -50 to -60 °C was slowly added a solution of DMSO (1.55 ml, 1.70 g, 21.7 mmol, 2.36 eq.) in CH₂Cl₂ (5 ml) at such a rate that the internal temperature did not rise above -50 °C. After 2 min the alcohol **I** (3.0 g, 9.20 mmol, 1.0 eq.) in CH₂Cl₂ (12 ml) was added over a period of 5 min and stirred for 15 min. Then NEt₃ (6.65 ml, 4.82 g, 47.7 mmol, 5.18 eq.) was added in a dropwise fashion and after an additional 5 min the reaction mixture was warmed to room temperature. After 1 h at room temperature, water (50 ml) was added and the aqueous layer was extracted with CH₂Cl₂ (3x20 ml). The combined organic layers were washed with brine (50 ml), dried (Na₂SO₄) and the solvents were removed in vacuo. The crude product was purified by flash chromatography (Cy/EtOAc 20:1) to give the aldehyde **II** (2.94 g, 9.06 mmol, 98%) as a colorless, crystalline solid. Analytical data for the title compound: **mp**: 55 °C; **¹H-NMR** (400 MHz, CDCl₃): δ = 1.42 (s, 3H), 1.80-1.88 (m, 1H), 2.14 (s, 3H), 2.21 (s, 3H), 2.25 (s, 3H), 2.27-2.32 (m, 1H), 2.51-2.66 (m, 2H), 4.70 (s, 2H), 7.33-7.43 (m, 3H), 7.49-7.51 (m, 2H), 9.65 (s, 1H); **¹³C-NMR** (100 MHz, CDCl₃): δ = 11.9, 12.0, 12.9, 20.3, 21.6, 27.8, 74.8, 80.5, 117.8, 123.2, 126.2, 127.7, 127.9 (2C), 128.5 (2C), 128.7, 137.9, 147.5, 149.3, 204.3; [**α**]_D²⁰: +10.8° (c = 1.10 in CHCl₃).

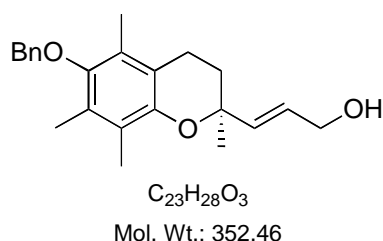
(S, E)-Ethyl-3-(6-benzyloxy)-2,5,7,8-tetramethyl-3,4-dihydro-2H-chromen-2-yl)acrylate



(8)

To a solution of ethyl 2-(diethoxyphosphoryl)acetate (1.10 g, 4.93 mmol, 2.0 eq.) in DME (6 ml) was added at 0 °C *n*-BuLi (3.65 ml, 4.93 mmol, 2.0 eq., 1.35 M in hexane). After 30 min at room temperature the reaction mixture was cooled to 0 °C and a solution of aldehyde **II** (0.80 g, 2.46 mmol, 1.0 eq.) in DME (10 ml) was added. The reaction was stirred for an additional 29 h at room temperature before water (50 ml) was added. The aqueous layer was extracted with TBME (3x15 ml), the combined organic layers were washed with water (20 ml), brine (20 ml) and dried (Na₂SO₄). The solvents were removed in vacuo to furnish the analytical pure title compound **8** (0.94 g, 2.38 mmol, 97 %) as a colorless, crystalline solid. Analytical data for the title compound: **mp**: 101 °C; **¹H-NMR** (400 MHz, CDCl₃): δ = 1.30 (dd, 3H, *J* = 7.3, 7.3 Hz), 1.47 (s, 3H), 1.86-1.93 (m, 1H), 1.99-2.05 (m, 1H), 2.15 (s, 3H), 2.19 (s, 3H), 2.25 (s, 3H), 2.45-2.53 (m, 1H), 2.61-2.68 (m, 1H), 4.20 (qq, 2H, *J* = 7.3, 7.3 Hz), 4.72 (s, 2H), 5.92 (d, 1H, *J* = 15.5 Hz), 6.97 (d, 1H, *J* = 15.5 Hz), 7.33-7.43 (m, 3H), 7.50-7.51 (m, 2H); **¹³C-NMR** (100 MHz, CDCl₃): δ = 11.9, 12.0, 12.9, 14.2, 20.8, 26.4, 31.7, 60.4, 74.7, 75.1, 117.3, 120.0, 122.7, 126.0, 127.7, 127.8 (2C), 128.3, 128.5 (2C), 138.0, 147.3, 148.7, 151.1, 166.6; [α]_D²⁰: +83.1° (c = 1.00 in CHCl₃); **CHN** calcd. C: 76.11, H: 7.66, found C: 75.81, H: 7.90.

(S)-(E)-3-(6-benzyloxy)-2,5,7,8-tetramethyl-3,4-dihydro-2H-chromen-2-yl)-prop-2-en-1-ol (III)

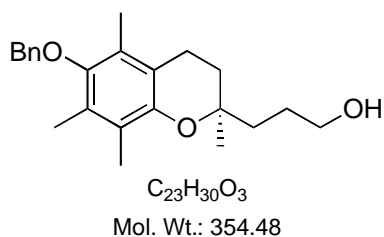


To a solution of ester **8** (2.20 g, 5.58 mmol, 1.0 eq.) in CH₂Cl₂ (40 ml) was added over 20 min at -78 °C DIBAL-H (16.70 ml, 16.72 mmol, 3.0 eq., 1 M in CH₂Cl₂). After 2 h sat. aqueous NH₄Cl-solution (9 ml) and Et₂O (30 ml) were added.

The reaction mixture was allowed to warm to room temperature and stirred for an additional 2h. The resulting suspension was filtered through Celite and rinsed with CH₂Cl₂ (40 ml). The layers were separated and the organic layer was washed with sat. aqueous NH₄Cl-solution (40 ml) and brine (40 ml). Then the organic layer was dried (Na₂SO₄) and the solvents removed in vacuo to furnish the title compound **III** (1.92 g, 5.44 mmol, 98%) as a colorless, crystalline solid. Analytical data for the title compound: **mp**: 78-79 °C; **¹H-NMR** (300 MHz, CDCl₃): δ = 1.25 (t, 1H, *J* = 5.9 Hz), 1.41 (s, 3H), 1.78-1.87 (m, 1H), 1.90-1.98 (m, 1H), 2.14 (s, 3H), 2.15 (s, 3H), 2.22 (s, 3H), 2.45-2.65 (m, 2H), 4.12 (dd, 2H, *J* = 5.8, 2.9 Hz), 4.70 (s,

2H), 5.69-5.81 (m, 2H), 7.30-7.42 (m, 3H), 7.48-7.50 (m, 2H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): $\delta = 11.9, 12.0, 12.9, 20.9, 27.1, 32.1, 63.2, 74.7, 74.9, 117.7, 122.3, 126.0, 127.7, 127.8, 127.8$ (2C), 128.1, 128.5 (2C), 135.5, 138.1, 147.8, 148.5; $[\alpha]_{\text{D}}^{20}$: $+48.8^\circ$ ($c = 1.10$ in CHCl_3); **CHN** calcd. C: 78.37, H: 8.00, found C: 78.23, H: 8.14.

(S)-3-(6-Benzyloxy)-2,5,7,8-tetramethyl-3,4-dihydro-2H-chromen-2-yl)propan-1-ol (IV)

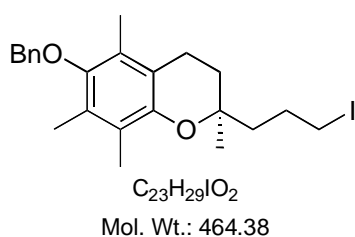


To a solution of the unsaturated alcohol **III** (176 mg, 0.50 mmol, 1.0 eq.) in TBME (2.5 ml) was added PtO_2 (10 mg, 8 mol%) and stirred under an atmosphere of H_2 . After 24 h the reaction mixture was filtered through $\text{MgSO}_4/\text{Celite}$ and rinsed with TBME (10 ml). The solvents were removed to give the title compound **IV** (170 mg, 0.48 mmol, 95%) as a

colorless oil. Analytical data for the title compound:

$^1\text{H-NMR}$ (300 MHz, CDCl_3): $\delta = 1.45$ (s, 3H), 1.61-1.91 (m, 7H), 2.12 (s, 3H), 2.19 (s, 3H), 2.24 (s, 3H), 2.61-2.67 (m, 2H), 3.68 (td, 2H, $J = 6.0, 3.0$ Hz), 4.72 (s, 2H), 7.33-7.43 (m, 3H), 7.51-7.52 (m, 2H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): $\delta = 11.9, 12.0, 12.9, 20.6, 23.7, 27.0, 31.5, 36.1, 63.3, 74.5, 74.7, 117.5, 123.0, 126.1, 127.7, 127.8$ (2C), 128.1, 128.5 (2C), 138.0, 147.7, 148.4; $[\alpha]_{\text{D}}^{20}$: -1.2° ($c = 1.01$ in CHCl_3); **CHN** calcd. C: 77.93, H: 8.53, found C: 77.86, H: 8.66.

(S)-6-Benzyloxy-2-(3-iodopropyl)-2,5,7,8-tetramethyl-3,4-dihydro-2H-chromene (9)

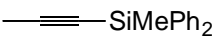


To an ice-cooled suspension of Ph_3PI_2 (448 mg, 0.87 mmol, 1.1 eq.) and imidazole (118 mg, 1.74 mmol, 2.2 eq.) in CH_2Cl_2 (3 ml) was added a solution of alcohol **IV** (280 mg, 0.79 mmol, 1.0 eq.) in CH_2Cl_2 (2 ml). After addition the mixture was allowed to warm to room temperature and was stirred for an

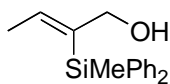
additional 18 h. The reaction mixture was filtered through Celite and rinsed with CH_2Cl_2 (3 ml). After removal of the solvents the crude product was purified by flash chromatography (PE \rightarrow PE/TBME 4:1) to give the title compound **9** (336 mg, 0.72 mmol, 92 %, $ee = 99\%$) as a colorless, crystalline solid. Analytical data for the title compound: **mp**: 39-41 $^\circ\text{C}$; $^1\text{H-NMR}$ (400 MHz, CDCl_3): $\delta = 1.26$ (s, 3H), 1.63-1.75 (m, 2H), 1.75-1.88 (m, 2H), 1.99-2.06 (m, 2H), 2.10 (s, 3H), 2.17 (s, 3H), 2.23 (s, 3H), 2.62 (t, 2H, $J = 6.88$ Hz), 3.16-3.28 (m, 2H), 4.71 (s, 2H), 7.34-7.42 (m, 3H), 7.49-7.51 (m, 2H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): $\delta = 7.4, 11.9, 12.0, 12.9, 20.6, 23.9, 28.2, 31.6, 40.8, 74.2, 74.8, 117.4, 123.0, 126.1, 127.7, 127.8$ (2C),

128.2, 128.5 (2C), 138.1, 147.6, 148.5; $[\alpha]_D^{21}$: -2.3° ($c = 1.05$ in CHCl_3); **CHN** calcd. C: 59.49, H: 6.29, found C: 59.64, H: 6.22; **HPLC** (Chiralpak AD, *n*-Hept/*i*-PrOH 100/1, 210 nm, 0.8 ml/min, 15 °C): t_R [(*R*)] = 8.44 min, t_R [(*S*)] = 9.91 min.

Diphenylmethyl-(prop-1-ynyl)-silane (**10**)

 To a solution of freshly distilled *Z/E*-1-bromopropene (1.81 g, 15.0 mmol, 1.5 eq.) in THF (10 ml) was added at -78°C *n*-BuLi (18 ml, 29.0 mmol, 2.9 eq., 1.60 M in hexane) in a dropwise fashion. After stirring for an additional 2.5 h the suspension was treated with diphenylmethylsilylchloride (2.40 g, 10.0 mmol, 1.0 eq., 97%) and stirred for 2 h before the mixture was warmed to room temperature. The mixture was stirred for 15 h, then sat. aqueous NH_4Cl -solution (20 ml) and water (40 ml) were added. The aqueous layer was extracted twice with TBME (20 ml) each. The combined organic layers were washed with water (2x20 ml), brine (20 ml) and dried (MgSO_4). The solvents were removed in vacuo and the crude product was filtered through ALOX N (activity IV) and rinsed with Et_2O . Removal of the solvents and distillation (200 °C/0.1 mbar) furnished the title compound **10** (2.32 g, 9.81 mmol, 98%) as a colorless liquid. Analytical data for the title compound: **$^1\text{H-NMR}$** (300 MHz, CDCl_3): $\delta = 0.67$ (s, 3H), 1.99 (s, 3H), 7.36-7.37 (m, 6H), 7.63-7.65 (m, 4H); **$^{13}\text{C-NMR}$** (100 MHz, CDCl_3): $\delta = 1.7, 5.2, 80.2, 106.6, 127.9$ (4C), 129.6 (2C), 134.5 (4C), 135.9 (2C); **CHN** calcd. C: 81.30, H: 6.82, found C: 81.07, H: 6.88.

(*Z*)-2-(Diphenylmethyl-silyl)-but-2-en-1-ol (**V**)

 A solution of DIBAL-H (2.35 ml, 1.87 g, 13.1 mmol, 1.2 eq.) in Et_2O (7 ml) at 0°C was treated with diphenylmethyl-(prop-1-ynyl)-silane (**10**) (2.59 g, 10.93 mmol, 1.0 eq.). The mixture was allowed to warm to room temperature and then heated to reflux for 2.5 h until the TLC showed quantitative hydroalumination. The reaction mixture was cooled to -5°C and MeLi (8.30 ml, 13.1 mmol, 1.2 eq., 1.6 M in Et_2O) was slowly added. After addition the reaction was allowed to warm to room temperature and it was stirred for an additional hour before cooled to 0°C again. The reaction mixture was transferred via syringe over 30 min to a cooled suspension of paraformaldehyde (2.60 g, 87.7 mmol, 8.0 eq., dried over P_2O_5) in Et_2O (7 ml). After addition the suspension was allowed to warm to room temperature and stirred for 55 h before it was poured into aq. HCl (20 ml, 1M). The suspension was filtered through Celite and rinsed with TBME (40 ml). The solution was diluted with water (20 ml), extracted with TBME (3x20 ml),

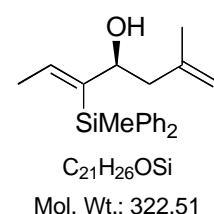
washed with brine (20 ml) and dried over Na₂SO₄. The solvents were removed in vacuo and the crude product was purified by flash chromatography (Cy/EtOAc 15:1) to give the desired alcohol **V** (2.14 g, 7.97 mmol, 73 %, E/Z < 2:98) as a clear, colorless liquid. Analytical data for the title compound: ¹H-NMR (400 MHz, CDCl₃): δ = 0.73 (s, 3H), 1.10 (t, 1H, *J* = 5.5 Hz), 1.60 (d, 3H, *J* = 6.9 Hz), 4.15 (m, 2H), 6.55 (q, 1H, *J* = 7.0 Hz), 7.31-7.39 (m, 6H), 7.53-7.56 (m, 4H); ¹³C-NMR (100 MHz, CDCl₃): δ = -2.3, 18.5, 69.3, 128.0 (4C), 129.3 (2C), 134.9 (4C), 136.6 (2C), 136.7, 141.9; CHN calcd. C: 76.07, H: 7.51, found C: 75.84, H: 7.54.

(Z)-2-(Diphenylmethyl-silyl)-but-2-enal (**11**)



To a suspension of Dess-Martin-periodinane (3.80 g, 8.94 mmol, 1.2 eq.) in CH₂Cl₂ (20 ml) was added dropwise a solution of allyl alcohol **V** (2.00 g, 7.45 mmol, 1.0 eq.) in CH₂Cl₂ (15 ml). After 1 h the reaction mixture was poured into NaOH (70 ml, 1M) and stirred for 5 min at room temperature. The organic layer was washed with NaOH (20 ml, 1 M), water (20 ml) and brine (20 ml). After drying over Na₂SO₄ the solution was filtered through Na₂SO₄/Celite-Pad (1:3) to remove suspended particles. The solvents were removed in vacuo to furnish the desired aldehyde **11** (1.96 g, 7.37 mmol, 99%) as a colorless, isomerically pure liquid. The aldehyde was used without further purification. (Note: The aldehyde **11** is only stable for a few days at -30 °C and under exclusion of light!). Analytical data for the title compound: ¹H-NMR (300 MHz, CDCl₃): δ = 0.79 (s, 3H), 1.71 (d, 3H, *J* = 7.2 Hz), 7.31-7.51 (m, 11H), 9.62 (s, 1H); ¹³C-NMR (75 MHz, CDCl₃): δ = -2.0, 19.0, 128.0 (4C), 129.4 (2C), 134.7 (4C), 135.0, 135.9, 141.6, 167.6, 199.0.

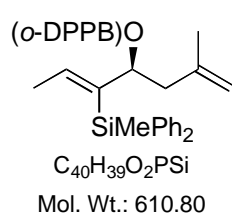
(S)-(Z)-2-methyl-5-(diphenylmethylsilyl)-hepta-1,5-dien-4-ol (**12**)



The above obtained aldehyde **11** (1.96 g, 7.37 mmol, 1.0 eq.) was immediately dissolved in THF (10 ml) and added to a preformed catalyst solution consisting of (*S*)-BINAP (462 mg, 0.75 mmol, 0.1 eq.) and AgOTf (193 mg, 0.75 mmol, 0.1 eq.) in THF (50 ml). The reaction mixture was stirred under exclusion of light at room temperature. After 5 min the solution was cooled to -20 °C and tributyl-(2-methylallyl)-stannane (5.48 g, 22.35 mmol, 3.0 eq.) was added via syringe over 5 min. The reaction mixture was stirred for 4 h before it was treated with the preformed catalyst solution of (*S*)-BINAP (462 mg, 0.75 mmol, 0.1 eq.) and AgOTf (193 mg, 0.75 mmol, 0.1 eq.) in THF (10 ml) again. After the reaction was stirred for 5 d at -20 °C, the brownish solution was poured into aq. HCl (100 ml, 1N) and stirred for

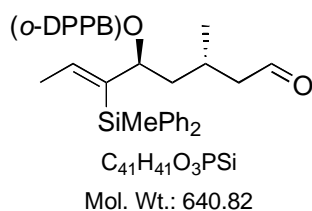
30 min at room temperature. The mixture was filtered through Celite, the aqueous layer was extracted with TBME (3x30 ml) and the combined organic layers were washed with sat. aqueous NaHCO₃-solution (30 ml), brine (30 ml) and dried over Na₂SO₄. Removal of the solvents and purification by flash chromatography (Cy/EtOAc 20:1) delivered the desired alcohol **12** (2.05 g, 6.35 mmol, 85%, >97% *ee*) as a colorless liquid. Analytical data for the title compound: ¹H-NMR (400 MHz, CDCl₃): δ = 0.77 (s, 3H), 1.40 (s, 3H), 1.63 (d, 3H, *J* = 7.3 Hz), 1.74 (d, 1H, *J* = 2.2 Hz), 2.00 (dd, 1H, *J* = 13.7, 10.3 Hz), 2.21 (dd, 1H, *J* = 13.3, 2.2 Hz), 4.25 (d, 1H, *J* = 10.3 Hz), 4.63 (m, 1H), 4.76-4.77 (m, 1H), 6.76 (qd, 1H, *J* = 7.1, 1.3 Hz), 7.33-7.41 (m, 6H), 7.54-7.59 (m, 4H); ¹³C-NMR (100 MHz, CDCl₃): δ = -1.5, 18.6, 21.4, 47.4, 72.3, 113.6, 127.9 (4C), 129.2 (2C), 135.1 (4C), 136.8, 136.9, 138.8, 138.9, 143.2; [α]_D²⁰: -64.8° (c = 1.00, CHCl₃); CHN calcd. C: 78.21, H: 8.13, found C: 77.99, H: 8.24; HPLC (Chiracel OD-H, *n*-Hept/*i*-PrOH 200/1, 220 nm, 0.8 ml/min, 25 °C): t_R [(*S*)] = 11.24 min, t_R [(*R*)] = 12.45 min.

(*S*)-(*Z*)-2-methyl-5-(diphenylmethylsilyl)-hepta-1,5-dien-4-yl-2-(diphenylphosphino)-benzoate (13**)**



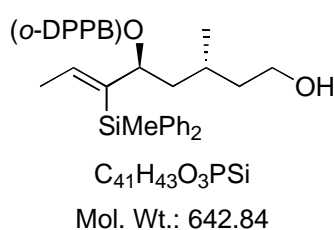
To a solution of (*S*)-(*Z*)-2-methyl-5-(diphenylmethylsilyl)-hepta-1,5-dien-4-ol (**12**) (700 mg, 2.17 mmol, 1.0 eq.) and *o*-DPPBA (864 mg, 2.82 mmol, 1.3 eq.) in CH₂Cl₂ (12 ml) was added DMAP (345 mg, 2.82 mmol, 1.3 eq.) and DCC (492 mg, 2.39 mmol, 1.1 eq.). The yellow suspension was stirred for 40 h at room temperature, filtered through a Celite-Pad and rinsed subsequently with CH₂Cl₂ (20 ml). After removal of the solvents the crude product was purified by flash chromatography (Cy/EtOAc 40:1) to furnish the title compound **13** (1.14 g, 1.86 mmol, 86%) as slightly yellow, resinous foam. Analytical data for the title compound: ¹H-NMR (400 MHz, CDCl₃): δ = 0.69 (s, 3H), 1.28 (s, 3H), 1.43 (d, 3H, *J* = 6.9 Hz), 2.16 (dd, 1H, *J* = 14.1, 3.4 Hz), 2.25 (dd, 1H, *J* = 14.1, 9.4 Hz), 4.52 (m, 1H), 4.58 (m, 1H), 5.45 (dd, 1H, *J* = 9.4, 3.4 Hz), 6.48 (q, 1H, *J* = 6.9 Hz), 6.87-6.92 (m, 1H), 7.26-7.35 (m, 17H), 7.50-7.54 (m, 5H), 7.98-8.01 (m, 1H); ¹³C-NMR (100 MHz, CDCl₃): δ = -1.8, 18.7, 21.7, 44.5, 76.6, 113.1, 127.9 (4C), 128.1, 128.4 (d, 2C, *J*_{C,P} = 5.8 Hz), 128.5 (d, 2C, *J*_{C,P} = 8.7 Hz), 129.1 (2C), 130.6, 131.7, 133.8, 134.0, 134.2 (d, 2C, *J*_{C,P} = 3.0 Hz), 134.3, 135.1 (2C), 135.2 (2C), 136.3, 136.4, 136.6, 138.3, 138.4, 138.6, 139.9 (2C), 140.8, 141.1, 142.0; ³¹P-NMR (121 MHz, CDCl₃): δ = -4.20; [α]_D²⁰: +3.8° (c = 1.1 in CHCl₃); CHN calcd. C: 78.66, H: 6.44, found C: 78.40, H: 6.40.

(4*S*,6*S*)-(Z)-6-methyl-3-(diphenylmethylsilyl)-8-oxooct-2-en-4-yl-2-(diphenylphino)-benzoate (14)



To a solution of $Rh(CO)_2acac$ (6.7 mg, 0.025 mmol, 0.02 eq.) in toluene (2 ml) was added $P(OPh)_3$ (32.1 mg, 0.10 mmol, 0.08 eq.) and stirred at room temperature. The primarily intense yellow solution faded after 10 min. At this time the ester **13** (790 mg, 1.29 mmol, 1.0 eq.) in toluene (10 ml) was added and the reaction mixture was then transferred into a well-dried, argon-purged autoclave. The argon atmosphere was removed by pressurizing/depressurizing cycle (three times 5 bar H_2/CO), and finally the autoclave was pressurized with 40 bar H_2/CO and heated in an oil bath to 40 °C for 9 d. Subsequently the autoclave was cooled to room temperature, depressurized and the solution was filtered through a silica-pad and rinsed with TBME. The solvents were removed in vacuo and purification by flash chromatography (Cy/EtOAc 40:1) yielded the aldehyde **14** (671 mg, 1.04 mmol, 81%, *anti:syn* 91:9) as a colorless resinous foam. Analytical data for the title compound: ^1H-NMR (400 MHz, $CDCl_3$): δ = 0.40 (d, 3H, J = 6.4 Hz), 0.72 (s, 3H), 1.23 (ddd, 1H, J = 14.1, 9.8, 2.6 Hz), 1.47 (s, 3H), [1.48 (s, 3H)], 1.58 (ddd, 1H, J = 14.3, 10.4, 3.9 Hz), 1.88-1.97 (m, 1H), 2.02 (ddd, 1H, J = 16.1, 7.3, 2.5 Hz), (2.11 (ddd, 1H, J = 15.9, 6.0, 2.2 Hz), 5.38 (d, 1H, J = 9.1 Hz), 6.46 (q, 1H, J = 6.8 Hz), [6.51 (q, 1H, J = 6.9 Hz)], 6.93-6.98 (m, 1H), 7.28-7.40 (m, 18H), 7.52-7.56 (m, 4H), [8.03-8.05 (m, 1H)], 8.07-8.10 (m, 1H), [9.33 (m, 1H)], 9.58 (t, 1H, J = 2.2 Hz); $^{13}C-NMR$ (100 MHz, $CDCl_3$): δ = -2.1, 18.3, 18.6, 25.0, 26.9 (2C), 42.8, [49.1], 51.1, 76.2, 127.7 (d, 4C, $J_{C,P}$ = 2.9 Hz), 128.2, 128.4 (d, 2C, $J_{C,P}$ = 7.3 Hz), 128.6 (d, 2C, $J_{C,P}$ = 4.3 Hz), 129.2, 130.7, 131.8, 133.8, 134.0 (d, $J_{C,P}$ = 4.3 Hz), 134.2, 134.3, [134.5], [134.7], 135.0 (2C), 135.1 (4C), 136.3 (d, $J_{C,P}$ = 4.4 Hz), 136.5, 138.1, 138.2, 138.4, 139.7, 140.3, 140.6, 165.9 (d, $J_{C,P}$ = 2.9 Hz), 202.5; $^{31}P-NMR$ (121 MHz, $CDCl_3$): δ = - 4.49 [- 4.53]; the data in squared brackets correspond to the minor diastereomer; $[\alpha]_D^{21}$: -10.7° (c = 1.13 in $CHCl_3$); **CHN** calcd. C: 76.84, H: 6.45, found C: 76.84, H: 6.73.

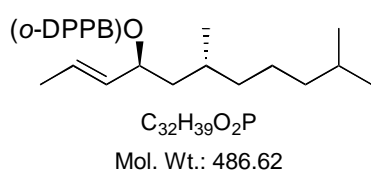
(4*S*,6*R*)-(Z)-8-hydroxy-6-methyl-3-(diphenylmethylsilyl)-oct-2-en-4-yl-2-(diphenylphosphino)benzoate (15)



To a solution of aldehyde **14** (192 mg, 0.30 mmol, 1.0 eq.) in MeOH (3 ml) was added $NaBH_4$ (12.5 mg, 0.33 mmol, 1.1 eq.) in one portion at 0 °C. After 30 min the reaction was quenched with water (25 μ l, 5 eq.). Removal of the solvents delivered the crude

¹H-NMR (400 MHz, C₆D₆): δ = 0.52 (d, 3H, *J* = 6.6 Hz), 0.79 (s, 3H), 0.85 (d, 3H, *J* = 0.8 Hz), 0.87 (d, 3H, *J* = 0.8 Hz), 1.06-1.26 (m, 6H), 1.33 (m, 1H), 1.42-1.49 (m, 1H), 1.44 (dd, 3H, *J* = 7.0, 0.6 Hz), 1.58-1.88 (m, 1H), 1.86 (ddd, 1H, *J* = 13.5, 10.2, 3.6 Hz), 5.72 (m, 1H), 6.58 (qd, 1H, *J* = 6.8, 1.0 Hz), 6.91 (td, 1H, *J* = 7.0, 1.5 Hz), 6.99 (td, 1H, *J* = 7.0, 1.3 Hz), 7.02-7.08 (m, 6H), 7.11-7.13 (m, 1H), 7.16-7.23 (m, 6H), 7.36-7.43 (m, 4H), 7.68-7.73 (m, 4H), 8.22 (m, 1H); **¹³C-NMR** (100 MHz, C₆D₆): δ = -1.76, 18.5, 18.8, 22.7, 22.8, 25.0, 27.1, 28.2, 38.2, 39.5, 43.9, 77.0, 127.8 (d, 4C, *J* = 1.7 Hz), 128.1 (2C), 128.3 (d, 4C, *J* = 1.6 Hz), 128.6 (d, 2C, *J* = 1.9 Hz), 128.7 (d, 2C, *J* = 2.6 Hz), 129.3 (2C), 130.9 (d, 2C, *J* = 2.9 Hz), 131.8, 134.3, 134.5, 134.9, 135.4 (2C), 135.6 (2C), 136.8, 137.0, 138.1, 138.2, 139.2, 139.6, 166.0; **³¹P-NMR** (161 MHz, C₆D₆): δ = -4.77 [-4.84]; the data in squared brackets correspond to the minor diastereomer; **[α]_D²⁰**: -2.5° (c = 1.03 in CHCl₃); **HRMS** [CI (M-Ph)] calcd. 605.3005, found 605.3004.

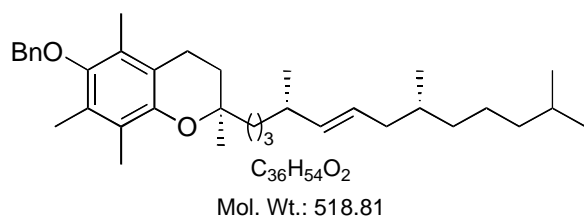
(4*S*,6*R*)-(E)-6,10-methylundec-2-en-4-yl-2-(diphenylphosphino)benzoate (17)



To a solution of olefin **16** (349 mg, 0.51 mmol, 1.0 eq.) in DMSO (5 ml) were added consecutively KF (180 mg, 3.06 mmol, 6 eq.), KHCO₃ (105 mg, 1.02 mmol, 2.0 eq.) and TBAF (1.30 ml, 1.27 mmol, 2.5 eq., 1M in THF). The reaction mixture was heated to 35 °C. After 6 h the reaction mixture was allowed to cool to room temperature over night. The reaction mixture was diluted with TBME (5 ml), cooled to 0 °C and then quenched with water (5 ml). The layers were separated and the aqueous layer was extracted with TBME (3 x 5 ml), washed with brine (20 ml) and dried over MgSO₄. The solvents were removed in vacuo and the crude product was purified by flash chromatography (toluene/Cy 2:1) to provide the ester **17** (191 mg, 0.39 mmol, 77%) as a light yellow resin. Analytical data for the title compound: **¹H-NMR** (400 MHz, C₆D₆): δ = 0.86 (d, 3H, *J* = 6.5 Hz), 0.87 (d, 3H, *J* = 0.8 Hz), 0.88 (d, 3H, *J* = 0.8 Hz), 1.02-1.30 (m, 7H), 1.42 (ddd, 3H, *J* = 6.1, 1.5, 0.6 Hz), 1.47 (sept, 1H, *J* = 6.6 Hz), 1.54-1.60 (m, 1H), 1.76 (ddd, 1H, *J* = 13.0, 9.5, 5.0 Hz), 5.32 (ddq, 1H, *J* = 15.1, 7.2, 1.6 Hz), 5.61 (dq, 1H, *J* = 15.1, 6.1, 0.9 Hz), 5.71 (m, 1H), 6.90 (m, 1H), 6.98 (m, 1H), 7.03-7.10 (m, 7H), 7.35-7.40 (m, 4H), 8.20 (m, 1H); **¹³C-NMR** (100 MHz, C₆D₆): δ = 17.7, 19.6, 22.7, 22.8, 24.8, 28.2, 29.4, 37.6, 39.5, 42.3, 74.4, 127.7 (2C), 128.0 (2C), 128.2 (2C), 128.52, 128.59, 128.6 (d, 2C, *J*_{C,P} = 1.5 Hz), 128.7 (d, 2C, *J*_{C,P} = 1.2 Hz), 129.0, 130.6, 131.8, 134.2, 134.4, 134.6, 134.8, 139.4, 166.1; **³¹P-NMR** (161 MHz, C₆D₆): δ = -4.45 [-4.51]; the data in squared brackets correspond to the minor

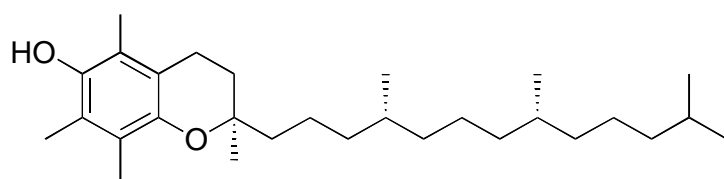
diastereomer; $[\alpha]_D^{20}$: -16.0° ($c = 1.03$ in CHCl_3); **CHN** calcd. C: 78.98, H: 8.08, found C: 79.01, H: 7.97.

(R)-6-(benzyloxy)-2,5,7,8-tetramethyl-2-((4S,8R,E)-4'-8'-12'-trimethyltridec-5-enyl)-3,4-dihydro-2H-chromene (18)



To a solution of *t*-BuLi (0.32 ml, 0.54 mmol, 3.36 eq., 1.7 M in pentane) in Et_2O (0.30 ml) was added at -85°C a solution of iodide **9** (119 mg, 0.26 mmol, 1.60 eq.) in Et_2O (0.6 ml) over a period of 1.5 h in a dropwise fashion with a syringe-pump. After complete conversion (TLC), freshly prepared magnesiumbromide-etherate (1.3 eq. based on iodide, 0.33 mmol dibromomethane, 1.00 mmol Mg, 1 ml Et_2O) was added to the white suspension. After addition the reaction was warmed to -50°C , stirred for 10 min before the reaction mixture was allowed to warm slowly to room temperature. The prepared Grignard-solution was then added over a period of 15 min to a yellow solution of ester **17** (79 mg, 0.16 mmol, 1.00 eq.) and $\text{CuBr}\cdot\text{SMe}_2$ (16.5 mg, 80 μmol , 0.5 eq.) in Et_2O (5 ml) at room temperature. The yellow solution with sallow yellow precipitate was stirred over night. Subsequently the reaction was quenched with sat. aqueous NH_4Cl -solution (5 ml) and aqueous NH_3 (1 ml, 10%). The aqueous layer was extracted with Et_2O (3x5 ml) and dried over MgSO_4 . The solvents were removed in vacuo and the crude product was purified by flash chromatography (Cy/toluene 4:1) to provide the title compound **18** (65 mg, 0.12 mmol, 78%) as colorless oil. Analytical data for the title compound: **$^1\text{H-NMR}$** (400 MHz, CDCl_3): $\delta = 0.85$ (d, 3H, $J = 6.5$ Hz), 0.86 (d, 3H, $J = 0.8$ Hz), 0.88 (d, 3H, $J = 0.8$ Hz), 0.97 (d, 3H, $J = 6.7$ Hz), 1.06-1.17 (m, 3H), 1.24 (s, 3H), 1.26-1.65 (m, 11H), 1.72-1.86 (m, 3H), 1.95-2.02 (m, 1H), 2.05-2.12 (m, 1H), 2.11 (s, 3H), 2.17 (s, 3H), 2.22 (s, 3H), 2.59 (t, 2H, $J = 6.8$ Hz), 4.70 (s, 2H), 5.24 (ddt, 1H, $J = 15.1, 7.4, 0.9$ Hz), 5.33 (dt, 1H, $J = 15.5, 6.8$ Hz), 7.32-7.42 (m, 3H), 7.49-7.52 (m, 2H); **$^{13}\text{C-NMR}$** (100 MHz, CDCl_3): $\delta = 11.9, 12.0, 12.9, 19.6, 20.7, 21.1, 21.5, 22.7, 22.8, 24.0, 24.9, 28.0, 31.3, 33.3, 36.8, 37.7, 39.4, 39.9, 74.8, 74.9, 77.8, 117.6, 123.0, 126.0, 127.1, 127.2, 127.7, 127.8, 128.0, 128.5, 129.1, 136.9, 137.6, 138.1, 148.0, 148.2$; $[\alpha]_D^{20}$: $+12.5^\circ$ ($c = 1.50$ in CHCl_3); **HRMS** calcd. 518.4129, found 518.4123.

(2*R*, 4'*R*, 8'*R*)- α -Tocopherol (**1**)

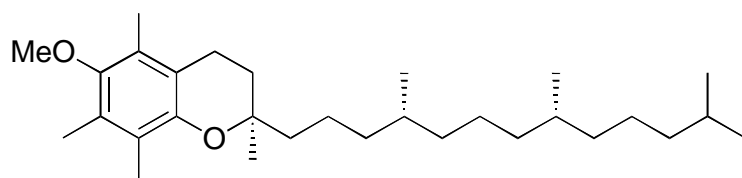


C₂₉H₅₀O₂
Mol. Wt.: 430.71

To a solution of olefin **18** (24 mg, 46.4 μ mol, 1.0 eq.) in EtOH (1 ml) was added freshly activated Raney-Ni (ca. 50 mg) and stirred under an atmosphere of H₂ over night at room temperature. The suspension was then filtered through a pad of MgSO₄ and washed with ethanol. The solvents were removed in vacuo and the crude product was purified by flash chromatography (Cy/EtOAc 5:1) to give the desired title compound **1** (18.2 mg, 42.2 μ mol, 91%) as a colorless oil. Analytical data for the title compound: ¹H-NMR (500 MHz, CDCl₃): δ = 0.83-0.87 (m, 12H), 1.02-1.32 (m, 21H), 1.22 (s, 3H), 1.78 (m, 2H), 2.11 (s, 6H), 2.15 (s, 3H), 2.60 (t, 2H, *J* = 7.0 Hz), 4.15 (s, 1H); ¹³C-NMR (125 MHz, CDCl₃): δ = 11.3, 11.8, 12.3, 19.7, 19.8, 20.8, 21.1, 22.7, 22.8, 23.8, 24.5, 24.9, 28.0, 31.6, 32.8, 32.9, 37.3, 37.52, 37.55, 37.57, 39.4, 39.9, 74.6, 117.4, 118.5, 121.0, 122.7, 144.6, 145.6; [α]_D²⁰: +1.3° (c = 0.85 in EtOH); HRMS: calcd. 430.3819, found 430.3811.

Determination of configuration of C-4' and C-8'

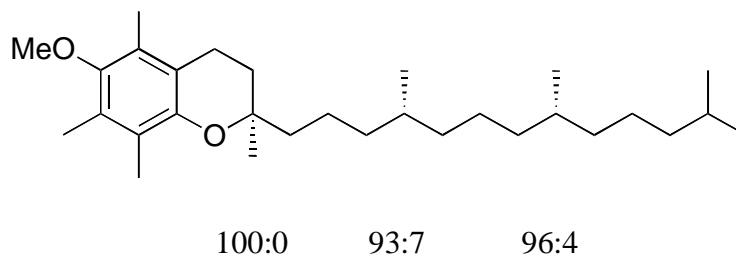
Preparation of the methylated (2*R*, 4'*R*, 8'*R*)- α -Tocopherol (**19**)



C₃₀H₅₂O₂
Mol. Wt.: 444.73

To a solution of α -tocopherol (**1**) (16 mg, 0.037 mmol, 1.0 eq.) in DME (0.30 ml) was added KOH (0.30 ml, 0.371 mmol, 10.0 eq., 50% in H₂O) and after 5 min dimethyl sulfate (18 μ l, 0.187 mmol, 5.0 eq.) was added dropwise to the reaction mixture. After 2 h the solvents were removed in vacuo (150 \rightarrow 15 mbar) and the crude mixture was treated with water (4 ml) and the aqueous layer was extracted with hexane (2x4 ml) and dried over MgSO₄. The solvents were removed in vacuo to provide the methyl ether **19** (16.6 mg, 0.037 mmol, quant.) as a yellowish oil. This oil was subjected to the analytics without any further purification. Analytical data for the title compound: ¹H-NMR (500 MHz, CDCl₃): δ = 0.83-0.87 (m, 12H), 1.03-1.56 (m, 21H), 1.23 (s, 3H), 1.78 (m, 2H), 2.08 (s, 3H), 2.13 (s, 3H), 2.18 (s, 3H), 2.57 (t, 2H, *J* = 7.0 Hz), 3.62 (s, 3H); ¹³C-NMR (125 MHz, CDCl₃): δ = 11.7, 11.8, 12.6, 19.7, 19.8, 20.7, 21.1, 22.7, 22.8, 24.0, 24.5, 24.9, 28.0, 31.6, 32.8, 32.9, 37.3, 37.52, 37.55, 37.6,

39.4, 40.1, 60.5, 74.6, 117.4, 118.2, 120.0, 122.9, 147.8, 149.4; **HPLC** (Chiracel OD 250 x 4.6 mm, *n*-hexane, 220 nm, 1.5 ml/min, 25 °C): t_R [**R, S, S**] = 30.06 min, t_R [**R, R, S**] = 33.73 min, t_R [**R, R, R**] = 40.10 min, t_R [**R, S, R**] = 46.08 min.



In accordance with literature reference the assignment of the configuration for C-2 is 100:0, for C-4 is 93:7 and for C-8 is 96:4 which correspond to a total concentration of >90% of pure (*R, R, R*)- α -tocopherol.

III Literature

- [1] G. E. Keck, E. J. Enholm, J. B. Yates, M. R. Wiley *Tetrahedron* **1985**, *41*, 4079-4094.
- [2] J. E. Hoots, T. B. Rauchfuss, D.-A. Wroblewski *Inorg. Synth.* **1982**, *21*, 175-179.
- [3] B. Wirz, R. Barner, J. Hübscher, *J. Org. Chem.* **1993**, *58*, 3980-3984.
- [4] R. Barner, J. Hübscher, J. J. Daly, P. Schönholzer, *Helv. Chim. Acta* **1981**, *64*, 915-938.
- [5] R. Barner, J. Hübscher, *Helv. Chim. Acta* **1983**, *66*, 880-890.
- [6] H. W. J. Cressman, J. R. Thirtle, *J. Org. Chem.* **1966**, *31*, 1279-1281.
- [7] H. Mayer, W. Vetter, J. Metzger, R. Rüegg, O. Isler, *Helv. Chim. Acta* **1967**, *50*, 1168-1178.
- [8] R. Barner, M. Schmid, *Helv. Chim. Acta* **1979**, *62*, 2384-2399.
- [9] N. Cohen, R. J. Lopresti, G. Saucy, *J. Am. Chem. Soc.* **1979**, *101*, 6710-6716.
- [10] N. Cohen, R. J. Lopresti, C. Neukom, *J. Org. Chem.* **1981**, *46*, 2445-2450.