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Enantioselective Palladium-Catalyzed Total Synthesis of Vitamin E by Employing a Domino Wacker–Heck Reaction

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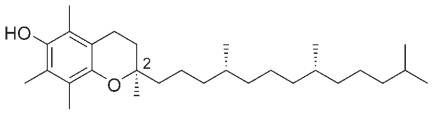
Dedicated to Professor Gyula Schneider on the occasion of his 75th birthday

Abstract: An enantioselective total synthesis of vitamin E in which a novel palladium-catalyzed domino reaction was employed as the key step is described. This reaction allows the formation of the chiral chroman framework and the concurrent introduction of part of the side chain of vitamin E. The sequence comprises an enantioselective Wacker cyclization and a subsequent Heck reaction. Accordingly, reaction of alkenylphenol **12** with methyl vinyl ketone (**13**) in the presence of catalytic amounts of $Pd(OTFA)_2$ (TFA = trifluoroacetate), the enantiopure ligand (*S*,*S*)-Bn-BOXAX (**8b**; Bn = benzyl, BOXAX = 2,2′-bis(oxazolyl)-1,1′-binaphthyl, and *p*-benzoquinone (**9**) as an oxidant gives access to chiral chroman **10** with an enantioselectivity of 97% *ee* in 84% yield. Chroman **10** is then converted into **24** by an aldol condensation reaction with (3*R*)-3,7-dimethyloctanal (**11**). Subsequent 1,2-addition of methyllithium, elimination of water, and hydrogenation yields vitamin E.

Keywords: asymmetric catalysis · domino reactions · Heck reactions · palladium · vitamins

Introduction

Vitamin E is one of the fat-soluble vitamins and a collective term for all tocopherols and tocotrienols. The vitamin E family consists of eight naturally occurring compounds which, depending upon the degree of methylation on their aromatic ring, are specified as α-, β-, γ- and δ-tocopherol and -tocotrienol, respectively. All are derivatives of 6-chromanol with a stereogenic center at C-2. The tocopherols have a saturated 16-carbon side chain with two stereogenic centers, whereas the tocotrienols have an unsaturated 16-carbon side chain with two *E*-configured double bonds (for example, α-tocopherol (**1**), α-tocotrienol (**2**)).[1] α-Tocopherol (**1**), which has the *R* configuration at all stereogenic centers, has the most pronounced biological activity. It acts as an antioxidant and is considered to be an essential protective factor against lipid peroxidation. In particular, **1** protects polyunsaturated fatty acids, other components of the cell membrane, and low-density lipoproteins (LDL) by capturing highly reactive free radicals formed in the body as by-products of normal oxidative metabolism.[2,3]



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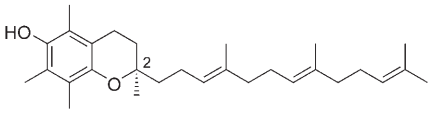

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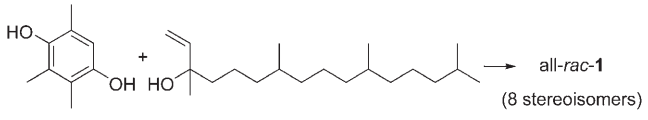
α-Tocopherol (*rac*-**1**) is produced industrially on a large scale, by means of an acid-catalyzed reaction of trimethylhydroquinone (**3**) with all-*rac*-isophytol (**4**), as a mixture of all eight possible stereoisomers (Scheme 1).[4]



3 **4**

Scheme 1. Industrially used synthesis of racemic α-tocopherol (all-*rac*-**1**) by reaction of trimethylhydroquinone (**3**) with all-*rac*-isophytol (**4**).

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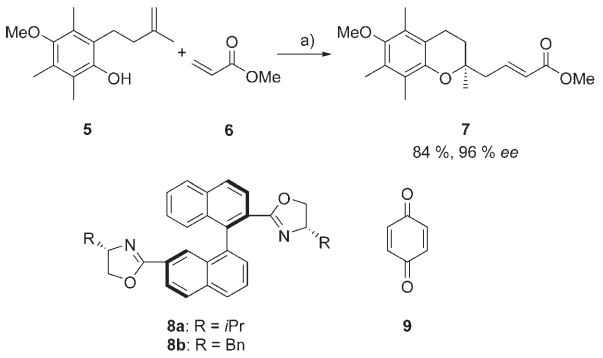
Recent studies have shown that 2*S*-configured tocopherols have no antioxidant effect in biological systems because they are not accepted as substrates by the α-tocopherol transfer protein (TTP), which is responsible for the transport of vitamin E into the tissue. On the other hand, the configuration of the stereogenic centers in the side chain appears to have no influence on the antioxidant effect.[5] As a result, *rac*-**1** exhibits a maximum of 50% of the biological activity of (*R*,*R*,*R*)-**1**. Therefore, there is considerable interest in the development of an efficient process for the enantioselective synthesis of vitamin E with special attention to the configuration of stereogenic center C-2.

Several enantioselective approaches to the synthesis of **1** based on resolution of the products, the use of enantiopure natural building blocks, auxiliary-controlled reactions, and asymmetric oxidations have been described.[6] In addition, a palladium-catalyzed asymmetric allylic alkylation reaction to construct the chiral chroman framework has been employed.[6a,b,d] We have developed asymmetric syntheses of the chiral chroman moiety by using a selective allylation of an alkyl methyl ketone and a Sharpless dihydroxylation as key steps.[6c,e,g–k] However, all these methods are not efficient enough for an industrial approach. Following these results, we have recently shown that the chiral chroman moiety in vitamin E can be prepared in a much more efficient way, with concurrent introduction of a part of the side chain, by using a novel enantioselective domino Wacker–Heck process (Scheme 2).[7–9] Thus, reaction of **5** with

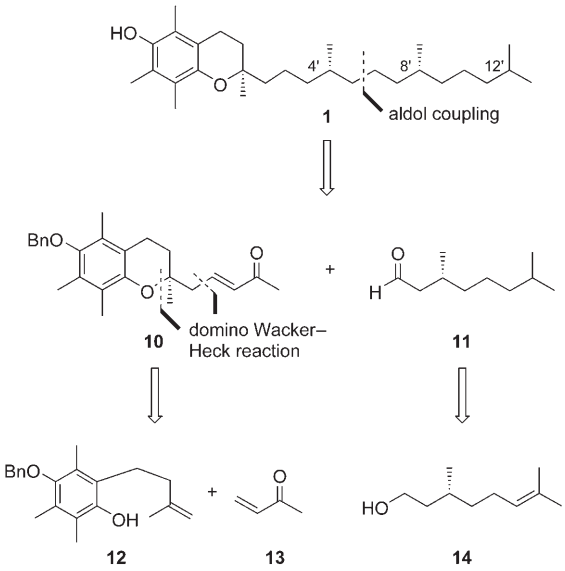


Scheme 2. Synthesis of chiral chroman **7**. Reagents and conditions: $Pd(OTFA)_2$, (*S*,*S*)-*i*Pr-BOXAX (**8a**), *p*-benzoquinone (**9**), CH_2Cl_2, RT, 3.5 d.

methyl acrylate (**6**), in the presence of catalytic amounts of $Pd(OTFA)_2$ and the enantiopure ligand BOXAX[10] (**8a**), led to the formation of **7** with an enantioselectivity of 96% *ee* in 84% yield. Here, we present the total synthesis of α-tocopherol (**1**) that was achieved by using the newly developed enantioselective domino Wacker–Heck reaction.

Results and Discussion

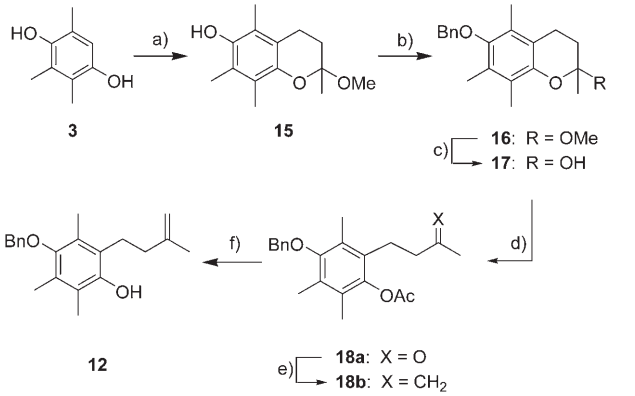
Preparation of α-tocopherol (**1**) using **7** did not seem appropriate because the acidic conditions required for cleavage of the methyl ether moiety in **7** might lead to a partial isomerization of the stereogenic center at C-2. We therefore focused on a new intermediate, **10**, which contains a benzyl protecting group that can be removed under milder conditions, and a methyl carbonyl moiety that can be used directly in an aldol reaction. Thus, retrosynthetic analysis of **1** gives intermediate **10** and (3*R*)-3,7-dimethyloctanal (**11**) (Scheme 3). Further disassembly of **10** gives the hydroqui-



Scheme 3. Retrosynthetic analysis of α-tocopherol (**1**).

none derivative **12**, which in turn can be prepared from trimethylhydroquinone (**3**) and methyl vinyl ketone (**13**). As previously outlined, we envisioned the introduction of stereogenic center C-2 into **1** by the catalytic enantioselective domino Wacker–Heck reaction of **12**, whereas stereogenic center C-8′ originates from (*R*)-citronellol (**14**).

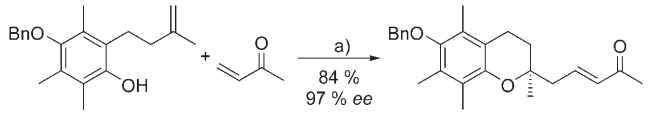
Alkenyl phenol **12** was prepared by using a multistep reaction sequence (Scheme 4). First, trimethylhydroquinone (**3**) was reacted with methyl vinyl ketone (**13**) in the presence of trimethyl orthoformate to give **15**, which was benzyl-



Scheme 4. Synthesis of alkene **12**. Reagents and conditions: a) **13**, $HC(OMe)_3$, H_2SO_4, MeOH, RT, 2 d, 94%; b) BnCl, K_2CO_3, acetone, RT, 24 h, 97%; c) HCl, acetone, 80°C, 88%; d) Ac_2O, pyridine, RT, 20 h, then 70°C, 4 h, 94%; e) $TiCl_4/Zn/CH_2Br_2$, CH_2Cl_2, RT, 2 h, 88%; f) NaOMe, MeOH, RT, 3 h, 88%.

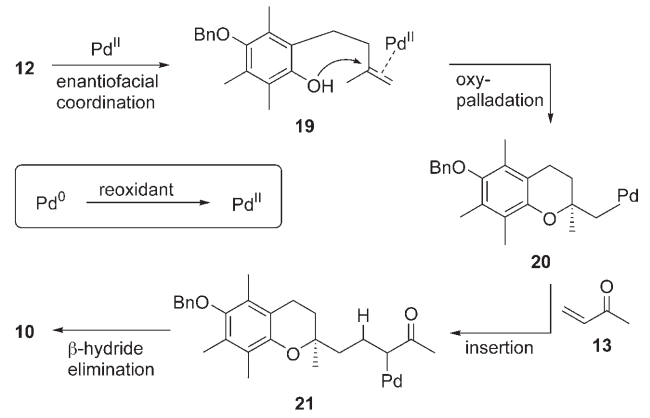
ated at the phenolic hydroxyl group to form **16**.[11] Subsequently, the acetal moiety in **16** was cleaved with hydrochloric acid to afford **17**. Exploiting the keto–enol tautomerism of **17**, phenyl ester **18** was prepared in 94% yield by using acetic anhydride dissolved in pyridine. Ultimately, formation of the double bond using the Lombardo reagent,[12] followed by Zemplén saponification afforded desired substrate **12** in six steps with an overall 56% yield based on **3**.

The domino reaction of benzyl-protected phenol **12** and methyl vinyl ketone (**13**) dissolved in dichloromethane in the presence of catalytic amounts of $Pd(OTFA)_2$, the chiral ligand (*S*,*S*)-Bn-BOXAX (**8b**), and *p*-benzoquinone (**9**) as a reoxidant afforded key intermediate **10** with 97% *ee* in 84% yield (Scheme 5).



Scheme 5. Synthesis of chiral chroman **10**. Reagents and conditions: $Pd(OTFA)_2$, (*S*,*S*)-Bn-BOXAX (**8b**), *p*-benzoquinone (**9**), CH_2Cl_2, RT, 3 d.

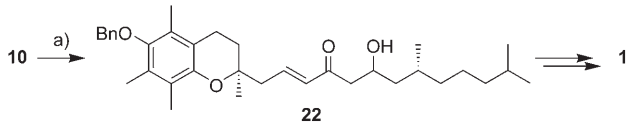
We assume that as the first step of the domino Wacker–Heck reaction, the chiral catalyst generated from $Pd(OTFA)_2$ and the enantiomerically pure ligand (*S*,*S*)-Bn-BOXAX (**8b**), coordinates enantiofacially to the aliphatic double bond in **12** (Scheme 6). Oxypalladation provides the



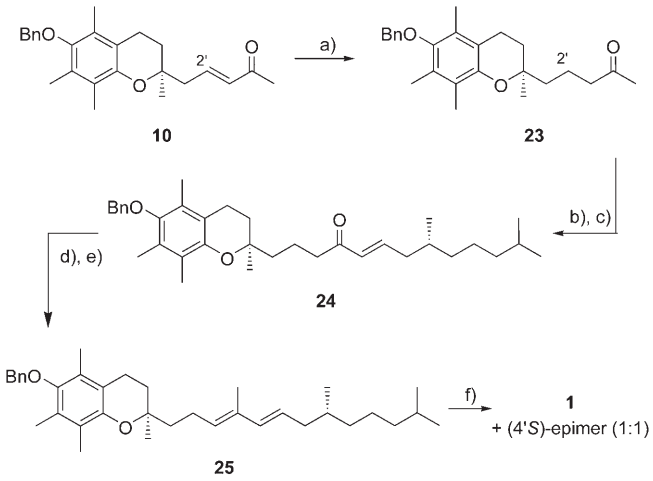
Scheme 6. Proposed mechanism for the domino Wacker–Heck reaction.

enantioselective formation of palladated chroman **20** with the correct absolute configuration at C-2 relative to **1**. Because β-hydride elimination is not possible, an intermolecular reaction with methyl vinyl ketone (**13**) to form **21** occurs, which can now undergo β-hydride elimination to yield **10**. To perform this reaction catalytically, Pd^0 must be reoxidized to Pd^{II}. To date, the best reagent for this reoxidation has been *p*-benzoquinone (**9**) because it does not interfere with the course of the reaction. Replacement of **9** by O_2/CuCl was unsuccessful because under these conditions oxidation of substrate **12** to give a *p*-benzoquinone derivative occurred.

We aimed to introduce the missing part of the side chain of α-tocopherol (**1**) that contains one stereogenic center by using (*R*)-citronellal. (*R*)-Citronellol (**14**), commercially available in a higher enantiomeric excess than (*R*)-citronellal, was employed as the substrate, which was then oxidized to (*R*)-citronellal. However, the aldol condensation of **10** with (*R*)-citronellal was not satisfying as a result of the formation of a byproduct from an intramolecular Prins reaction of (*R*)-citronellal. Therefore, for the coupling reaction with **10**, we used (3*R*)-3,7-dimethyloctanal (**11**), which was obtained from **14** by hydrogenation of the double bond followed by a Swern oxidation, with an overall yield of 92%. For the aldol reaction, **10** was transformed into the corresponding boron enolate by using $cHex_2BCl$ to give product **22** in an excellent yield of 90% (Scheme 7).[13] Unfortunately, **22** was not an ideal substrate for subsequent transformations. We therefore repeated the sequence by using chroman **23** containing a saturated side chain (Scheme 8).



Scheme 7. Synthesis of **22**. Reagents and conditions: a) iPr_2EtN, $cHex_2BCl$, Et_2O, −78 °C, 1 h, then **11**, −78 °C, 3 h, 90%.



Scheme 8. Synthesis of **1**. Reagents and conditions: a) $PtO_2{\cdot}H_2O$, H_2, EtOAc, RT, 30 min, 86%; b) iPr_2EtN, $cHex_2BCl$, Et_2O, −78 °C, 1 h, then **11**, −78 °C, 3 h; c) cat. *p*-TsOH, toluene, 60 °C, 30 min, 82% over two steps; d) MeLi, THF, −78 °C, 1 h; e) cat. *p*-TsOH, toluene, 60 °C, 30 min, 76% over two steps; f) Pd/C, H_2 (2 bar), EtOAc, RT, 30 min, 90%.

Saturated ketone **23** could easily be prepared from **10** by using $PtO_2{\cdot}H_2O/H_2$. Formation of the boron enolate of **23,** using iPr_2NEt and $cHex_2BCl$ at −78 °C followed by an aldol reaction with **11**, proceeded smoothly to give the corresponding aldol adduct, which was treated with catalytic amounts of *p*-toluenesulfonic acid (*p*-TsOH) dissolved in toluene to afford **24** in 82% yield over two steps. The last

three transformations for the synthesis of **1** included a 1,2-addition of methyllithium to the carbonyl moiety in **24** to give the corresponding tertiary alcohol, which was transformed into diene **25** in 76% over two steps by means of an acid-catalyzed elimination using *p*-TsOH. The final step was hydrogenation of the diene moiety in **25** with simultaneous deprotection of the benzylated phenolic hydroxyl group using hydrogen in the presence of catalytic amounts of Pd/C. In this reaction (2*R*,4′*R*,8′*R*)-α-tocopherol (**1**) was formed together with its (4′*S*)-epimer, as expected, in almost a 1:1 mixture in 90% total yield. To date, we have been unable to perform a stereoselective hydrogenation of the butadiene moiety in **25**, but Pfaltz and co-workers have recently demonstrated that trisubstituted alkenes can be hydrogenated with high enantioselectivity by using a new iridium-based catalyst.[14] However, it has been shown that the configuration of the stereogenic centers in the side chain have no influence on the bioactivity of vitamin E[5] so the diastereomeric mixture we have prepared should have the same antioxidant effect as the natural product.

Conclusion

In conclusion, we have developed a new total synthesis of vitamin E by using a novel enantioselective domino Wacker–Heck process as the key reaction step. This reaction not only allows the formation of the chroman framework with the necessary *R* configuration at stereogenic center C-2 with 97% *ee*, but also the introduction of a part of the side chain in 84% yield. Condensation with (3*R*)-3,7-dimethyloctanal (**11**) followed by reaction with methyllithium completed the synthesis.

Experimental Section

General: All reactions were performed under argon in flame-dried flasks. All solvents were dried and distilled prior to use by means of usual laboratory methods. All reagents obtained from commercial sources were used without further purification. Thin-layer chromatography (TLC) was performed on precoated silica gel SIL G/UV$_{254}$ plates (Macherey-Nagel GmbH & Co. KG), and silica gel 60 (0.032–0.063 mm, Merck) was used for column chromatography. Phosphomolybdic acid dissolved in methanol (PMA) or vanillin dissolved in methanolic sulfuric acid were used as staining reagents for TLC analysis. UV spectra were recorded, using CH_3CN or MeOH as solvents, on a Perkin–Elmer Lambda 2 spectrometer. IR spectra were recorded as KBr pellets or as films on a Bruker IFS 25 spectrometer. ^1H and ^{13}C NMR spectra were recorded with Mercury-200, VXR-200, Unity-300, Inova-500, Unity Inova-600 (Varian), or AMX 300 (Bruker) spectrometers. Chemical shifts are reported in ppm using tetramethylsilane (TMS) as the internal standard. Multiplicities of ^{13}C NMR peaks were determined with the attached proton test (APT) pulse sequence. Mass spectra were measured on a Finnigan MAT 95, TSQ 7000 or LCQ instrument. Elemental analysis was carried out by members of the Mikroanalytisches Labor, Institut für Organische und Biomolekulare Chemie, Georg-August-Universität Göttingen.

2-Methoxy-2,5,7,8-tetramethylchroman-6-ol (15): Concentrated sulfuric acid (0.5 mL) and methyl vinyl ketone (29.5 g, 400 mmol) were added dropwise to a stirring, degassed and ice-cooled solution of trimethyl-*p*-hydroquinone (**3**) (30.4 g, 200 mmol) and trimethyl orthoformate (27.0 g, 254 mmol) in methanol (120 mL). Stirring was continued for 2 d at room temperature, the mixture was then diluted with Et_2O (500 mL), washed with brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue recrystallized from methanol to yield **15** as colorless needles (44.2 g, 94%). M.p. 156°C; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 4.33$ (s, 1H; OH), 3.18 (s, 3H; OCH_3), 2.67–2.48 (m, 2H; 4-H_2), 2.16 (s, 6H; 5-CH_3, 7-CH_3), 2.12 (s, 3H; 8-CH_3), 1.84–1.72 (m, 2H; 3-H_2), 1.52 ppm (s, 3H; 2-CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 145.4$, 143.7 (C-6, C-8a), 122.1, 121.1, 118.7, 118.4 (C-4a, C-5, C-7, C-8), 97.2 (C-2), 48.8 (OCH_3), 31.9 (C-3), 23.1 (2-CH_3), 19.9 (C-4), 12.2, 11.6, 11.2 ppm (5-CH_3, 7-CH_3, 8-CH_3); IR (KBr): $\tilde{\nu}$? = 3452, 2986, 2946, 2882, 2836, 1638, 1546 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε) = 291 (3.484), 199 nm (4.658); MS (70 eV, EI): *m*/*z* (%): 236 (46) [M^+], 221 (3) [$M^+ - CH_3$], 205 (38) [$M^+ - OCH_3$], 189 (13) [$M^+ - C_2H_7O$], 164 (100) [$M^+ - C_4H_8O$]; HRMS: *m*/*z* calcd for $C_{14}H_{20}O_3$: 236.1412; found: 236.1412.

6-Benzyloxy-2-methoxy-2,5,7,8-tetramethylchroman (16): Benzyl chloride (31.5 g, 176 mmol) was added to a suspension of chromanol **15** (20.8 g, 88.0 mmol) and K_2CO_3 (26.7 g, 193 mmol) in degassed acetone (100 mL) and the mixture was stirred for 24 h at room temperature. After addition of water (500 mL), the mixture was extracted with Et_2O (3 × 200 mL) and the combined organic layers were washed with brine and dried over Na_2SO_4. Concentration under reduced pressure and column chromatography on silica gel (*n*-pentane/Et_2O 10:1) provided acetal **16** as a colorless oil (27.9 g, 97%). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.53$–7.30 (m, 5H; Ar-H), 4.69 (s, 2H; CH_2Ph), 3.23 (s, 3H; OCH_3), 2.74–2.51 (m, 2H; 4-H_2), 2.22, 2.17–2.15 (3 × s, 9H; 5-CH_3, 7-CH_3, 8-CH_3), 1.88–1.76 (m, 2H; 3-H_2), 1.55 ppm (s, 3H; 2-CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 148.9$ (C-6), 146.1 (C-8a), 137.9 (C-1′), 128.4 (C-3′, C-5′), 127.8 (C-4′), 127.7 (C-2′, C-6′), 127.6, 125.9, 122.6, 118.8 (C-4a, C-5, C-7, C-8), 97.3 (C-2), 74.6 (CH_2Ph), 48.9 (OCH_3), 31.8 (C-3), 23.1 (2-CH_3), 19.9 (C-4), 12.8, 11.9, 11.6 ppm (5-CH_3, 7-CH_3, 8-CH_3); IR (film): $\tilde{\nu} = 3030$, 2988, 2937, 1606, 1497, 1377 cm^1; UV (CH_3CN): λ_{max} (lg ε) = 283 (0.967), 201 nm (2.987); MS (70 eV, EI): *m*/*z* (%): 326 (20) [M^+], 295 (16) [$M^+ - OCH_3$], 235 (100) [$M^+ - Bn$], 91 (45) [Bn^+]; HRMS: *m*/*z* calcd for $C_{21}H_{26}O_3$: 326.1882; found: 326.1882.

6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ol (17): 0.1 N aqueous HCl (30 mL) was added to a solution of acetal **16** (22.3 g, 68.4 mmol) in acetone (120 mL) and then the solvent was distilled off at 80°C. After addition of acetone (80 mL), the process was repeated. The residue was dissolved in Et_2O (200 mL), and the obtained solution washed with water (150 mL), 2 N aqueous HCl (100 mL), brine, and dried over Na_2SO_4. Removal of the solvent under reduced pressure and recrystallization from Et_2O afforded chromanol **17** as colorless needles (18.2 g, 88%). M.p. 109°C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.53$–7.30 (m, 5H; Ar-H), 4.69 (s, 2H; CH_2Ph), 2.78–2.58 (m, 2H; 4-H_2), 2.49 (s, 1H; OH), 2.20, 2.19, 2.12 (3 × s, 9H; 5-CH_3, 7-CH_3, 8-CH_3), 1.90–1.79 (m, 2H; 3-H_2), 1.65 ppm (s, 3H; 2-CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 148.9$, 148.8 (C-6, C-8a), 137.8 (C-1′), 128.4 (C-3′, C-5′), 127.8 (C-4′), 127.7 (C-2′, C-6′), 128.3, 126.0, 124.0, 117.8 (C-4a, C-5, C-7, C-8), 95.4 (C-2), 74.7 (CH_2Ph), 31.4 (C-3), 28.7 (2-CH_3), 20.00 (C-4), 12.4, 12.0, 11.9 ppm (5-CH_3, 7-CH_3, 8-CH_3); IR (film): $\tilde{\nu} = 3379$, 3034, 1496 cm^{-1}.

Acetic acid 4-benzyloxy-2,3,5-trimethyl-6-(3-oxobutyl)phenyl ester (18a): A solution of chromanol **17** (21.3 g, 68.2 mmol) dissolved in pyridine (114 mL) was treated with acetic anhydride (19.8 mL, 210 mmol) and the resulting solution was stirred for 20 h at room temperature and then for 4 h at 70°C. The solvent was removed and the resulting residue recrystallized from ethanol to yield ketone **18a** as a colorless solid (22.7 g, 94%). M.p. 83°C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.51$–7.32 (m, 5H; Ar-H), 4.72 (s, 2H; CH_2Ph), 2.84–2.50 (m, 4H; 1″-H_2, 2″-H_2), 2.34 (s, 3H; 2′-H_3), 2.23, 2.22, 2.15 (3 × s, 9H; 2-CH_3, 3-CH_3, 5-CH_3), 2.02 ppm (s, 3H; 4″-H_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 208.0$ (C-3″), 169.8 (C-1′), 153.4 (C-4), 144.0 (C-1), 137.5 (C-1‴), 129.9 (C-6), 129.0 (C-5), 128.5 (C-3‴, C-5‴), 128.0 (C-4‴), 127.7 (C-3), 127.6 (C-2‴, C-6‴), 127.5 (C-2), 74.3 (CH_2Ph), 42.8 (C-2″), 29.9 (C-4″), 21.6 (C-1″), 20.6 (C-2′), 13.2, 13.1, 12.4 ppm (2-CH_3, 3-CH_3, 5-CH_3); IR (film): $\tilde{\nu} = 2982$, 2950, 2832, 1750, 1216 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε) = 314 (3.364), 264 (4.047), 200 nm (4.463); MS (70 eV, EI): *m*/*z* (%): 354 (10) [M^+], 263 (20) [$M^+ - Bn$], 221 (100) [$M^+ - Bn - Ac$]; HRMS: *m*/*z* calcd for $C_{21}H_{26}O_4$: 354.1831; found: 354.1831.

Acetic acid 4-benzyloxy-2,3,5-trimethyl-6-(3-methylbut-3-enyl)phenyl ester (18b): Ketone **18a** (6.86 g, 19.5 mmol) was added portionwise to an ice cooled solution of the Lombardo reagent[12] (174 mL, 58.0 mmol) dissolved in CH_2Cl_2 (70 mL). The resulting suspension was then stirred for 2 h at room temperature before saturated aqueous $NaHCO_3$ (400 mL) was added. The precipitate was filtered over Celite and washed with CH_2Cl_2 (3×500 mL). Water (1000 mL) was added to the filtrate and the mixture was extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography on silica gel (*n*-pentane/Et_2O 9:1) afforded alkene **18b** as a colorless solid (6.00 g, 88%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.50–7.31 (m, 5H; Ar-H), 4.74 (s, 2H; 4″-H_2), 4.73 (s, 2H; CH_2Ph), 2.80–2.40 (m, 2H; 1″-H_2), 2.34 (s, 3H; 2′-H_3), 2.20–1.90 (m, 2H; 2″-H_2), 2.27, 2.24, 2.00 (3×s, 9H; 2-CH_3, 3-CH_3, 5-CH_3), 1.79 ppm (s, 3H; 3″-CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=169.6 (C-1′), 153.3 (C-4), 145.8 (C-3″), 144.0 (C-1), 137.6 (C-1‴), 130.9 (C-6), 128.5 (C-3, C-2), 128.4 (C-3‴, C-5‴), 127.9 (C-4‴), 127.7 (C-2‴, C-6‴), 127.4 (C-5), 109.9 (C-4″), 74.3 (CH_2Ph), 37.4 (C-2″), 26.9 (C-1″), 22.4 (3″-CH_3), 20.6 (C-2′), 13.2, 13.1, 12.3 ppm (2-CH_3, 3-CH_3, 5-CH_3); IR (KBr): $\tilde{\nu}$=3485, 3074, 2967, 1750, 1647, 1454, 1209, 1010 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε)=268 (0.080), 200 nm (5.916); MS (70 eV, EI): *m*/*z* (%): 352 (40) [M^+], 310 (20) [M^+−Ac], 219 (100) [M^+−Bn−Ac]; HRMS: *m*/*z* calcd for $C_{23}H_{28}O_3$: 352.2038; found: 352.2083; elemental analysis calcd (%) for $C_{23}H_{28}O_3$ (352.40): C 77.32, H 7.65; found: C 78.38, H 8.01.

4-Benzyloxy-2,3,5-trimethyl-6-(3-methylbut-3-enyl)phenol (12): A 5.4 M NaOMe solution (0.53 mL, 1.71 mmol) was added dropwise to a solution of acetic ester **18b** (6.00 g, 17.1 mmol) dissolved in methanol (150 mL). The mixture was stirred for 3 h at room temperature and after consumption of the starting material, the pH was adjusted to pH 7 by careful addition of Amberlite® IR-120. The solvent was removed under reduced pressure and the crude product purified by using column chromatography on silica gel (PE/Et_2O 99:1→90:10) to yield **12** as a colorless solid (4.69 g, 88%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.53–7.30 (m, 5H; Ar-H), 4.80 (s, 2H; 4′-H_2), 4.69 (s, 2H; CH_2Ph), 4.50 (br s, 1H; OH), 2.80–2.72 (m, 2H; 1′-H_2), 2.20–2.10 (m, 2H; 2′-H_2), 2.25, 2.23, 2.15, (3×s, 9H; 3×Ar-CH_3), 1.81 ppm (s, 3H; 3′-CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=149.2 (C-4), 147.9 (C-1), 146.3 (C-3′), 137.8 (C-1″), 128.5 (C-3″, C-5″), 127.9 (C-4″), 127.7 (C-2″, C-6″), 127.1 (C-2, C-6), 124.9 (C-3), 120.4 (C-5), 110.1 (C-4′), 74.6 (CH_2Ph), 37.1 (C-2′), 26.0 (C-1′), 22.7 (3′-CH_3), 13.0, 12.3, 12.2 ppm (2-CH_3, 3-CH_3, 5-CH_3); IR (KBr): $\tilde{\nu}$=3438, 3065, 2967, 2915, 2873, 1646, 1455, 1375, 1329, 1262, 1156, 1087, 1069, 988, 886, 696 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε)=191.0 (5.371), 201.0 (5.229), 284.5 nm (1.398), MS (70 eV, EI): *m*/*z* (%): 310.3 (20) [M^+], 219 (100), [M^+−Bn]; HRMS: *m*/*z* calcd for $C_{21}H_{26}O_2$: 310.4299; found: 310.4299.

(2*S*)-5-(6-Benzyloxy-2,5,7,8,-tetramethylchroman-2-yl)-3-penten-2-one (10): A mixture of palladium trifluoroacetate (6.4 mg, 19.8 μmol) and (*S*,*S*)-Bn-BOXAX **8b** (44.6 mg, 77.9 μmol) dissolved in CH_2Cl_2 (0.1 mL, degassed) was stirred for 30 min at room temperature, then treated with *p*-benzoquinone (**9**, 84.9 mg, 0.785 mmol), and stirred for a further 10 min. A solution of **12** (60.4 mg, 0.195 mmol) and methyl vinyl ketone (**13**, 90.4 mg, 0.975 mmol) dissolved in CH_2Cl_2 (0.10 mL, degassed) was added and the mixture was stirred at room temperature for 3 d (TLC control). After consumption of the starting material, the mixture was treated with 1 N HCl (5 mL) and the aqueous phase extracted with Et_2O (3×10 mL). The combined organic phases were washed with 1 N NaOH solution (3×5 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (*n*-pentane/EtOAc 20:1) and chroman **10** was obtained as a colorless oil (62 mg, 0.165 mmol, 84%, 97% *ee*). The enantiomeric excess was determined by using HPLC on chiral stationary phase.[15] HPLC (OD Chiracel): wavelength 210 nm, flow 0.8 mL min^{-1}, eluent: hexane/isopropanol 97:3; t_R=19.09 min ((−)-**10**); t_R=28.31 min ((+)-**10**); *ee*=97%; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.53–7.30 (m, 5H; Ar-H), 6.90 (ddd, *J*=16.0, 16.0, 7.9 Hz, 1H; 4-H), 6.11 (d, *J*=16.0 Hz, 1H; 3-H), 4.69 (s, 2H; CH_2Ph), 2.62 (t, *J*=6.9 Hz, 2H; 4′-H_2), 2.57 (dd, *J*=14.1, 8.0 Hz, 1H; 5-H_b), 2.51 (dd, *J*=14.1, 7.4 Hz, 1H; 5-H_a), 2.27 (s, 3H; 1-H_3), 2.23, 2.17, 2.11 (3×s, 9H; 5′-CH_3, 7′-CH_3, 8′-CH_3), 1.83 (t, *J*=6.9 Hz, 2H; 3′-H_2), 1.29 ppm (s, 3H; 2′-CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=198.3 (C-2), 148.5 (C-8a′), 147.2 (C-6′), 143.6 (C-4), 137.8 (C-1″), 134.0 (C-3), 128.4 (C-3″, C-5″), 128.3 (C-7′), 127.8 (C-4″), 127.7 (C-2″, C-6″), 126.1 (C-5′), 123.0 (C-8′), 117.1 (C-4a′), 74.7 (CH_2Ph), 74.2 (C-2′), 42.5 (C-5), 31.4 (C-3′), 26.8 (C-1), 24.4 (2′-CH_3), 20.5 (C-4′), 11.8, 11.9, 12.8 ppm (5′-CH_3, 7′-CH_3, 8′-CH_3); IR (film): $\tilde{\nu}$=2927, 1674, 1455, 1253, 1088, 984.9 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε)=202.5 (4.749), 280.0 nm (3.374), 286.0 (3.380); MS (70 eV, EI): *m*/*z* (%): 378.3 (22) [M^+], 287.2 (100) [M^+−Bn]; HRMS: *m*/*z* calcd for $C_{25}H_{30}O_3$: 378.2195; found: 378.2195.

(2*S*)-5-(6-Benzyloxy-2,5,7,8,-tetramethylchroman-2-yl)pentan-2-one (23): PtO_2•H_2O (19.5 mg, 0.08 mmol, 4 mol% Pt) was added to a solution of enone **10** (725 mg, 1.92 mmol) dissolved in EtOAc (20 mL). The mixture was stirred for 30 min under 1 atm of hydrogen at room temperature and then filtered over Celite (rinsing with EtOAc). The filtrate was concentrated under reduced pressure and the crude material was purified by flash chromatography on silica gel (*n*-pentane/EtOAc 20:1) to give **23** as a colorless oil (624 mg, 86%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.56–7.28 (m, 5H; Ar-H), 4.69 (s, 2H; CH_2Ph), 2.60 (t, *J*=6.8 Hz, 2H; 4′-H_2), 2.46 (dt, *J*=7.1, 4.1 Hz, 2H; 3-H_2), 2.22, 2.17, 2.15 (3×s, 9H; 5′-CH_3, 7′-CH_3, 8′-CH_3), 2.11 (s, 3H; 1-H_3), 1.93–1.65 (m, 4H; 3′-H_2, 4-H_2), 1.65–1.47 (m, 2H; 5-H_2), 1.27 ppm (s, 3H; 2′-CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=208.9 (C-2), 148.1 (C-8a′), 147.6 (C-6′), 137.9 (C-1″), 128.4 (C-3″, C-5″), 128.0 (C-7′), 127.7 (C-4″), 127.6 (C-2″, C-6″), 126.0 (C-5′), 122.8 (C-8′), 117.4 (C-4a′), 74.6 (CH_2Ph), 74.5 (C-2′), 43.9 (C-5), 38.9 (C-3), 31.2 (C-3′), 29.8 (C-1), 23.7 (2′-CH_3), 20.5 (C-4′), 18.0 (C-4), 12.8, 11.9, 11.8 ppm (5′-CH_3, 7′-CH_3, 8′-CH_3); IR (film): $\tilde{\nu}$=2926, 1716, 1455, 1373, 1255, 1088, 735.4, 698.3 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε)=204.0 (4.747), 287.5 nm (3.367); MS (70 eV, EI): *m*/*z* (%): 378.3 (22) [M^+], 287.2 (100) [M^+−Bn)]; HRMS: *m*/*z* calcd for $C_{25}H_{32}O_3$: 380.5198; found: 380.5198.

(2′*R*,8*R*)-1-(6-Benzyloxy-2,5,7,8-tetramethylchroman-2-yl)-8,12-dimethyl-5-tridecen-4-one (24): *i*Pr_2NEt (339 mg, 2.61 mmol) and *c*Hex_2BCl (2 mL of an 1 M solution in hexane, 196 mmol) were added dropwise at −78 °C to a solution of methyl ketone **23** (497 mg, 1.31 mmol) dissolved in Et_2O (15 mL). The resulting white heterogeneous mixture was stirred for 30 min at −78 °C followed by slow addition of a solution of aldehyde **11** (419 mg, 2.61 mmol) dissolved in Et_2O (25 mL) over 15 min. The mixture was then stirred for 3 h at −78 °C before pH 7 buffer/MeOH (v/v 1:6) solution (5 mL) was added. The resulting clear solution was cooled to 0 °C and 30% H_2O_2/MeOH (v/v 1:2) solution (5 mL) was added. The ice bath was removed and the reaction was stirred at room temperature for 1 h. The solution was diluted with Et_2O (10 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product purified by using flash chromatography (*n*-pentane/EtOAc 20:1). *p*-Toluenesulfonic acid (45.1 mg, 0.237 mmol) was added to a solution of the latter aldol product (635 mg, 1.18 mmol) dissolved in toluene (10 mL). The resulting mixture was stirred at 60 °C for 30 min. Triethylamine (24 mg, 0.240 mmol) and Et_2O (10 mL) were added to the mixture and the organic phase was washed with H_2O (10 mL). The aqueous phase was extracted with Et_2O (3×5 mL) and the combined organic phases were washed with saturated aqueous $NaHCO_3$, brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product purified by flash chromatography on silica gel (*n*-pentane/EtOAc 4:1) to give **24** as a colorless oil (560 mg, 82% over two steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.60–7.30 (m, 5H; Ar-H), 6.95–6.74 (m, 1H; 6-H), 6.10 (d, *J*=15.8 Hz, 1H; 5-H), 4.72 (s, 2H; CH_2Ph), 2.74–2.48 (m, 4H; 1-H_2, 4′-H_2), 2.24, 2.19, 2.12 (3×s, 9H; 5′-CH_3, 7′-CH_3, 8′-CH_3), 2.31–1.99 (m, 2H; 3-H_2), 1.92–1.72 (m, 4H; 3′-H_2, 2-H_2), 1.72–1.46 (m, 4H; 7-H_2, 8-H, 12-H), 1.29 (s, 3H; 2′-CH_3), 1.38–1.06 (m, 8H; 1-H_2, 9-H_2, 10-H_2, 11-H_2), 0.89 (d, *J*=6.6 Hz, 3H; 8-CH_3), 0.88 ppm (d, 6H; *J*=6.5 Hz, 6H; 12-CH_3, 13-H_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=200.4 (C-4), 148.2 (C-8a′), 147.7 (C-6′), 146.3 (C-6), 138.0 (C-1″), 131.3 (C-5), 128.4 (C-3″, C-5″), 127.9 (C-7′), 127.7 (C-4″), 127.6 (C-2″, C-6″), 126.0 (C-5′), 122.8 (C-8′), 117.5 (C-4a′), 74.6 (CH_2Ph), 74.6 (C-2′), 40.3 (C-1), 39.9 (C-3), 39.1 (C-7), 39.1 (C-11), 36.9 (C-9), 32.6 (C-8), 31.2 (C-3′), 27.9 (C-12), 24.7 (C-10), 23.8 (2′-CH_3), 22.6 (C-13), 22.5 (12-CH_3), 20.6 (C-4′), 19.6 (8-CH_3), 18.4 (C-2), 12.8, 12.0, 11.8 ppm (5′-CH_3, 7′-CH_3, 8′-CH_3); IR (Film): $\tilde{\nu}$=2926, 1673, 1455, 1373, 1255, 1088, 733.6 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε)=204.0 (4.803), 282.0 nm (3.380), 287.5 (3.424); HRMS: *m*/*z* calcd for $C_{35}H_{52}O_4$: 536.7850; found: 536.7850.

(2*R*,8*R*′)-6-Benzyloxy-2,5,7,8-tetramethyl-2-(4,8,12-trimethyl-3,5-tridecadienyl)chroman (25): Enone **24** (700 mg, 1.35 mmol) was dissolved in Et_2O (10 mL) at −78 °C under argon and MeLi (1.6 M solution in Et_2O, 1 mL, 1.6 mmol) was added dropwise. The resulting mixture was stirred at this temperature for 1 h, quenched with ice water (5 mL), and then allowed to warm to room temperature. The layers were separated and the aqueous phase was extracted with Et_2O (3×10 mL). The combined organic extracts were washed with brine (10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was redissolved in toluene (10 mL). *p*-Toluenesulfonic acid (50.1 mg, 0.260 mmol) was added and the resulting mixture was stirred at 60 °C for 30 min. After addition of triethylamine (26 mg, 0.260 mmol) and Et_2O (10 mL), the organic phase was washed with H_2O (10 mL). The aqueous phase was extracted with Et_2O (3×5 mL), the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product purified by using flash chromatography on silica gel (*n*-pentane/EtOAc 50:1) to give **25** as colorless oil (532 mg, 76 % over two steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55–7.29 (m, 5H; Ar-H), 6.45–5.03 (m, 3H; 3-H, 5-H, 6-H), 4.69 (s, 2H; CH_2Ph), 2.63–2.53 (m, 2H; 4′-H_2), 2.22, 2.16, 2.10 (3×s, 9H; 5′-CH_3, 7′-CH_3, 8′-CH_3), 1.72 (s, 3H; 4-CH_3), 2.47–1.40 (m, 10H; 3′-H_2, 1-H_2, 2-H_2, 7-H_2, 8-H, 12-H), 1.27, 1.24 (s, 3H; 2′-CH_3), 0.85 (d, J = 6.4 Hz, 6H; 12-CH_3, 13-H_3), 1.38–0.80 ppm (m, 9H; 8-CH_3, 9-H_2, 10-H_2, 11-H_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 148.1 (C-8a′), 147.8 (C-6′), 138.7 (C-6), 138.0 (C-1″), 136.2 (C-4), 135.7 (C-5), 128.4 (C-3″, C-5″), 128.0 (C-7′), 127.7 (C-4″), 127.6 (C-2″, C-6″), 126.3 (C-5′), 126.0 (C-3), 122.9 (C-8′), 117.5 (C-4a′), 74.7 (CH_2Ph), 74.6 (C-2′), 40.4, 40.1 (C-2, C-7), 39.4 (C-1), 39.1 (C-11), 36.87 (C-9), 31.4 (C-3′), 27.9 (C-12), 24.8 (2′-CH_3), 22.6 (C-10), 22.6 (C-13, 12-CH_3), 20.7 (C-8), 20.6 (C-4′), 19.6 (8-CH_3), 12.8 (7′-CH_3), 12.3 (4-CH_3), 12.00 (8′-CH_3), 11.84, 11.82 ppm (5′-CH_3); IR (Film): $\tilde{\nu}$ = 2925, 1455, 1373, 1255, 1088, 732.5 cm^{-1}; UV (CH_3CN): λ_{max} ($\lg\varepsilon$) = 204.0 (4.803), 282.0 nm (3.380), 287.5 (3.424); HRMS: *m*/*z* calcd for $C_{36}H_{52}O_2$: 516.7969; found: 516.7969.

(2*R*,4′*RS*,8′*R*)-α-Tocopherol (1): Palladium on charcoal (24 mg, 10 mol %) was added to a degassed solution of diene **25** (97.0 mg, 0.188 mmol) dissolved in EtOAc (10 mL) and the reaction mixture was shaken for 30 min at room temperature under an atmosphere of hydrogen (2 bar). The solution was filtered over Celite, washed with EtOAc, and the filtrate was concentrated under reduced pressure. The crude material was purified by using flash chromatography on silica gel (*n*-pentane/EtOAc 20:1) to give **1** as a yellow oil as a 1:1 mixture together with (2*R*,4′*S*,8′*R*)-α-tocopherol (73.1 mg, 90 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.16 (s, 1H; OH), 2.59 (t, J = 6.9 Hz, 2H; 4-H_2), 2.14, 2.09 (2×s, 9H; 5-CH_3, 7-CH_3, 8-CH_3), 1.80 (dt, J = 13.5, 6.9 Hz, 1H; 3-H_b), 1.74 (dt, J = 13.4, 6.9 Hz, 1H; 3-H_a), 1.21 (s, 3H; 2-CH_3), 1.65–1.00 (m, 21H; 1′-H_2, 2′-H_2, 3′-H_2, 4′-H, 5′-H_2, 6′-H_2, 7′-H_2, 8′-H, 9′-H_2, 10′-H_2, 11′-H_2, 12′-H), 0.85 (d, J = 6.5 Hz, 6H; 12′-CH_3, 13-H_3), 0.85 (d, J = 6.4 Hz, 3H; 8′-CH_3), 0.83 ppm (d, J = 6.4 Hz, 3H; 4′-CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 146.3 (C-8a), 145.9 (C-6), 122.9 (C-8), 122.4 (C-7), 120.4 (C-5), 117.0 (C-4a), 74.79, 74.78 (C-2), 40.4 (C-1′), 40.3, 40.0 (C-11′), 38.32, 38.18 (C-3′), 38.17 (C-9′), 38.12, 38.11 (C-5′), 38.05, 38.04, 38.03 (C-7′), 33.46, 33.45 (C-8′), 33.36, 33.35 (C-4′), 32.43, 32.37 (C-3), 28.6 (C-12′), 25.49, 25.48 (C-10′), 25.06, 25.04 (C-6′), 24.13, 24.12, (2-CH_3), 22.98, 22.89(12′-CH_3, C-13), 21.7, 21.6 (C-2′), 21.3 (C-4), 20.1 (8′-CH_3), 20.0 (4′-CH_3), 12.2 (7-CH_3), 12.0 (8-CH_3), 11.8 ppm (5-CH_3); IR (KBr): $\tilde{\nu}$ = 2926, 1456, 1378, 1259, 1086 cm^{-1}; UV (CH_3CN): λ_{max} ($\lg\varepsilon$) = 201.5 (4.653), 293.5 nm (3.532); MS (70 eV, EI): *m*/*z* (%): 429.4 (10) [M^+], 205.2 (100) [$M^+ - C_{16}H_{33}$]; HRMS: *m*/*z* calcd for $C_{29}H_{80}O_2$: 430.7220; found: 430.7220.

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