# Total Synthesis of (*R*)- and (*S*)-*semi*-Vioxanthin

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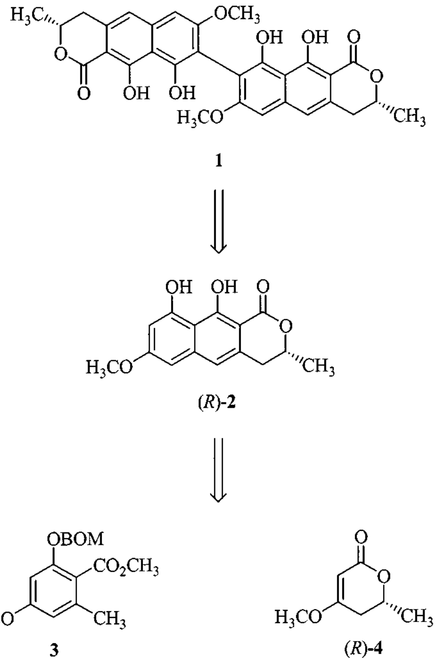
Compounds (*R*)- and (*S*)-*semi*-vioxanthin **2** were synthesized by a tandem Michael reaction of orsellinate **3** and the chiral Michael acceptors **4**. The key step for the formation of lactone (*R*)-**4** is a regio- and enantioselective, enzyme-catalyzed reduction of *tert*-butyl 3,5-dioxohexanoate (**5**) by an alcohol-dehydrogenase from *Lactobacillus brevis*. Compound (*S*)-**4** was synthesized by the Claisen condensation of *tert*-butyl acetate and ethyl (*S*)-3-hydroxy-butanoate (**8**). Cleavage of the benzyloxymethyl groups in the protected (*R*)- and (*S*)-*semi*-vioxanthins was achieved by hydrogenolysis to afford (*R*)-**2** and (*S*)-**2**, respectively.

## Introduction

More than 70 years ago, Pummerer et al.[1] found that the oxidation of *para*-cresol to an *ortho*-*para* coupled product, the Pummerer ketone, proceeds through phenolic radicals. Later on, Barton and Cohen[2] attributed the structures of many phenol-coupled natural products of higher plants to this radical mechanism. Since then, many efforts have been made to mimic the biosynthesis of those phenol-coupled metabolites, both chemically with oxidants[3] and biochemically with oxidizing enzymes.[4] In contrast to the biological systems, in which strict regio- and stereoselectivity are observed, all of these chemical and biochemical methods for oxidative phenol coupling have been deficient in regio- and stereoselective control. Recently, Lewis et al.[5] reported that lignan formation by means of oxidative phenol coupling is a two-enzyme process. They isolated an oxidase responsible for the single-electron transfer and a second enzyme that controls the regio- and stereoselective C−C bond formation.

It has been established independently by two groups[6,7] that the dimerization of preanthraquinones in fungi proceeds through oxidative phenol coupling. Our work is directed toward characterizing the enzymes responsible for this oxidative phenol coupling. For this reason, we have chosen the filamentous fungus *Penicillium citreo-viride*,[8] a producer of the dimeric metabolite vioxanthin **1** and its monomeric precursor (*R*)-*semi*-vioxanthin (*R*)-**2**. In order to develop an assay system, we set out to synthesize both enantiomers of *semi*-vioxanthin **2**.

The first synthesis of racemic *semi*-vioxanthin **2** was achieved by Yamaguchi et al.,[9] via a polyketide intermediate. For our purpose, we applied a strategy used by Deshpande and co-workers (Scheme 1),[10] also following previous synthetic strategies by Weinreb and Staunton.[11] Deshpande et al. synthesized *semi*-vioxanthin **2** in a racemic form by means of a tandem Michael reaction between an orsellinate and a cyclic Michael acceptor. Here we report on the first stereoselective synthesis of (*R*)- and (*S*)-*semi*-vioxanthin **2**.



Scheme 1. Retrosynthetic analysis of vioxanthin **1**

## Results and Discussion

Since the production of protected orsellinates is well known,[12,13] the decisive step is the formation of both enantiomers of Michael acceptor **4** in an enantiomerically pure form. Although (*S*)-*semi*-vioxanthin (*S*)-**2** has not so far been characterized as a natural product, the synthesis of both enantiomers of **2** is required so as to enable characterization of the as-yet-unknown enzymes and their enzyme activity.

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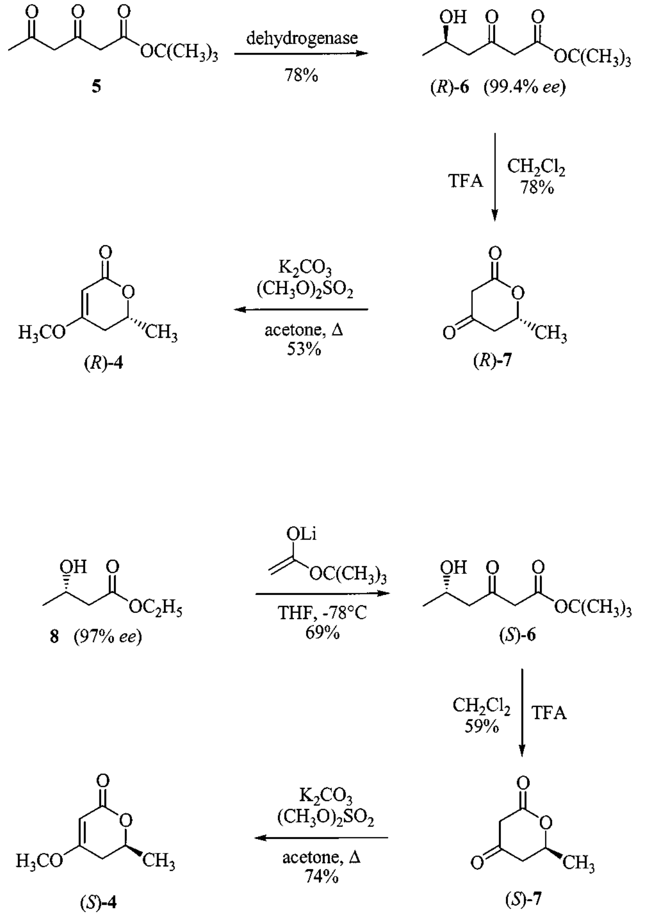
### Synthesis of the Chiral Michael Acceptors

For the synthesis of (*R*)-**4**, a method developed by Wolberg et al.[14] was used. The regio- and stereoselective enzymatic reduction of *tert*-butyl 3,5-dioxohexanoate (**5**)[15] with alcoholdehydrogenase from *Lactobacillus brevis* (*LB*ADH) afforded almost optically pure (*R*)-**6** (99.4% *ee*) in high yield. The hydroxy ketone (*R*)-**6** was lactonized to (*R*)-5,6-dihydro-4-hydroxy-6-methyl-2*H*-pyran-2-one [(*R*)-**7**] by hydrolysis with trifluoroacetic acid.[16] The synthesis was completed by *O*-methylation with dimethyl sulfate, affording (*R*)-5,6-dihydro-4-methoxy-6-methyl-2*H*-pyran-2-one [(*R*)-**4**] (Scheme 2).



Scheme 2. Synthesis of the enantiomerically pure Michael acceptors **4**

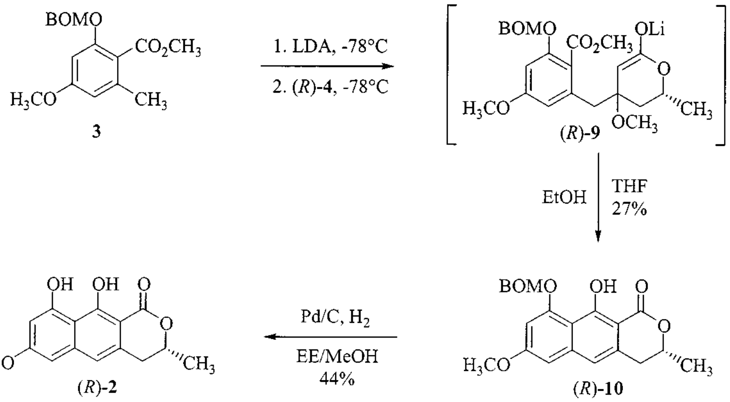
For the preparation of the (*S*)-enantiomer, a Claisen condensation of *tert*-butyl acetate and commercially available ethyl (*S*)-3-hydroxy-butanoate (**8**) (97% *ee*) − which is itself produced by bakers' yeast reduction of ethyl acetoacetate − was performed, giving *tert*-butyl (*S*)-5-hydroxy-3-oxohexanoate [(*S*)-**6**].[17] This compound was converted into pyranone (*S*)-**4** analogously to its enantiomer (Scheme 2).

These results demonstrate that the regioselective reduction of *tert*-butyl 3,5-dioxohexanoate (**5**) with an isolated enzyme, resulting in virtually enantiopure *tert*-butyl (*R*)-5-hydroxy-3-oxohexanoate [(*R*)-**6**] (99.4% *ee*), is advantageous in comparison to the more classical formation of ethyl (*S*)-3-hydroxy-butanoate [(*S*)-**8**] (97% *ee*) by whole-cell biotransformation of ethyl acetoacetate, followed by C−C bond elongation.

### Synthesis of (*R*)- and (*S*)-*semi*-Vioxanthin

The preparation of methyl 2,4-dihydroxy-6-methylbenzoate in a one-step procedure according to Chiarello and Joullié[12] was followed by a selective methylation of the hydroxyl group at the C-4 atom with iodomethane.[13] In order to protect the hydroxyl group at C-2, methyl 2-hydroxy-4-methoxy-6-methylbenzoate was converted into the corresponding sodium salt with sodium methoxide, and then benzyl chloromethyl ether and triethylamine were added. The benzyloxymethyl protecting group was chosen because it is stable under the conditions of the tandem Michael reaction and can be cleaved selectively.

The aromatic ring system of *semi*-vioxanthin **2** was built up through tandem Michael reactions of orsellinate **3** with pyranones (*R*)- and (*S*)-**4**, respectively. Methyl 2-benzyloxymethoxy-4-methoxy-6-methylbenzoate (**3**) was deprotonated with lithium diisopropylamide at −78 °C, to give the corresponding benzyl anion. The nucleophile then attacked the pyranone **4** in an exclusively 1,4-addition to give an intermediate enolate **9**. This enolate attacked the carboxyl carbon to provide the desired ring system **10**, after warming to room temperature. The β-methoxy moiety of the enone **4** increases its reactivity towards carbanions[11] and the spontaneous elimination of methanol after the tan-



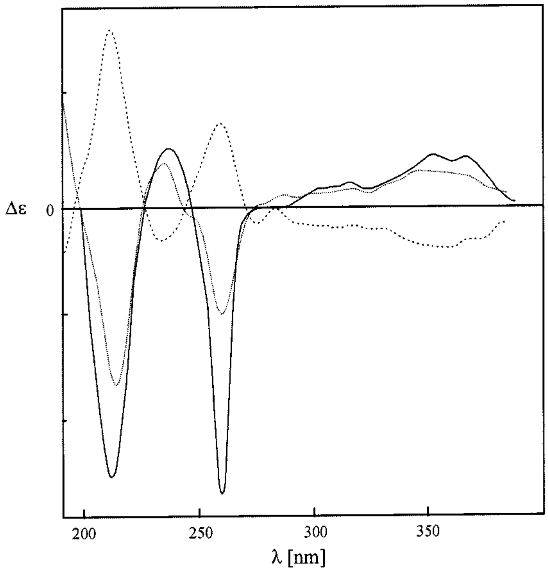
Scheme 3. Synthesis of (*R*)-*semi*-vioxanthin (*R*)-**2** by tandem Michael reaction of orsellinate **3** with Michael acceptor (*R*)-**4**

dem Michael reaction directly afforded the aromatic system. In this manner, benzyloxymethyl-protected (*R*)- and (*S*)-*semi*-vioxanthins **10** were prepared in 27% isolated yield (Scheme 3).

Selective cleavage of the benzyloxymethyl groups was achieved by hydrogenolysis with palladium on charcoal under a hydrogen atmosphere at ambient pressure to give (*R*)- and (*S*)-*semi*-vioxanthin **2** in 44% and 39% yield, respectively.

### Circular Dichroism

Comparison of the CD spectra of (*R*)-*semi*-vioxanthin [(*R*)-**2**] isolated from *Penicillium citreo-viride*[8] and synthetic (*R*)- and (*S*)-*semi*-vioxanthin **2**, with maxima at 215 nm and 266 nm (Figure 1), revealed the absolute configuration of the natural product to be *R*.



—— synthetic (*R*)-*semi*-vioxanthin
…… synthetic (*S*)-*semi*-vioxanthin
—— (*R*)-*semi*-vioxanthin isolated from *Penicillium citreo-viride*[8]

Figure 1. CD spectra of synthetic (solvent: trifluoroethanol) and naturally occurring (solvent: cyclohexane/5% dioxane) *semi*-vioxanthin **2**

## Conclusion

(*R*)- and (*S*)-*semi*-vioxanthin **2** have been prepared by two convergent, chemoenzymatic routes, that differ in the timing of their introductions of chiral characteristics and their enzymatic conversions. The decisive step is the highly efficient biotransformation to introduce the stereogenic centers into compounds **6** with excellent *ee*s. Future work will deal with the synthesis of vioxanthin **1** in order to set up an assay system necessary for the identification of the enzymes responsible for stereoselective oxidative phenol coupling.

## Experimental Section

**General remarks:** All reagents used were of analytical grade. Solvents were dried by standard methods if necessary. Methyl 2,4-dihydroxy-6-methylbenzoate,[12] methyl 2-hydroxy-4-methoxy-6-methylbenzoate,[13] **5**,[15] (*R*)-**6**[14] and (*S*)-**6**[17] were synthesized according to published procedures. TLC was carried out on aluminium sheets precoated with silica gel 60F$_{254}$ (Merck). Detection was accomplished by UV light (λ = 254 nm). Preparative column chromatography was carried out on silica gel 60 (Merck) (mesh size 40−63 μm). NMR spectra were recorded on an AMX 300 (Bruker Physik AG, Germany). Chemical shifts δ are reported in ppm relative to CHCl$_3$ ($^1$H, δ = 7.26) and CDCl$_3$ ($^{13}$C, δ = 77.0) as internal standard. GCMS spectra were determined on an HP 6890 series GC system fitted with an HP 5973 mass selective detector (Hewlett Packard; column HP-5MS, 30 m·250 μm; $T_{GC}$ (injector) = 250 °C, $T_{MS}$ (ion source) = 200 °C, time program (oven): $T_{0\,min}$ = 60 °C, $T_{3\,min}$ = 60 °C, $T_{14\,min}$ = 280 °C (heating rate 20 °C·min$^{-1}$), $T_{19\,min}$ = 280 °C). HRMS (EI) was performed on an A.E.I. MS 50 and elemental analysis on a Vario EL (Heraeus) at the Analytical Department, Chemische Institut der Universität Bonn. Optical rotations were measured on a polarimeter (Perkin−Elmer 241). Molar circular dichroic absorptions Δε are reported in cm$^2$·mmol$^{-1}$. CD spectra were recorded on a Jasco J-720 spectral polarimeter with 2,2,2-trifluoroethanol as solvent. Melting points were measured on a Büchi B-540 heating unit and are not corrected.

**Methyl 2-Benzyloxymethoxy-4-methoxy-6-methylbenzoate (3):**[18] To a solution of sodium methoxide (1.10 g, 20.20 mmol) in methanol (10 mL) was added methyl 2-hydroxy-4-methoxy-6-methylbenzoate (1.13 g, 5.77 mmol). The solvent was evaporated and the residue suspended in dry THF (20 mL). To this mixture were added triethylamine (1.6 mL, 11.54 mmol) and benzyl chloromethyl ether (2.0 mL, 8.66 mmol). After stirring overnight, the reaction mixture was washed with a saturated solution of NaHCO$_3$ (100 mL) and brine (100 mL). The aqueous phase was extracted with ethyl acetate (3 × 100 mL), the combined organic layers dried (Na$_2$SO$_4$) and the solvent evaporated under reduced pressure. The residue was purified by column chromatography (PE/EE = 5:1; $R_f$ = 0.22) to give **3** (1.70 g, 93%) as a colorless oil. − $^1$H NMR (300 MHz, CDCl$_3$): δ = 2.30 (s, 3 H, CH$_3$), 3.76 (s, 3 H, OCH$_3$), 3.89 (s, 3 H, OCH$_3$), 4.71 (s, 2 H, CH$_2$), 5.26 (s, 2 H, CH$_2$), 6.40 (d, $^4J$ = 2.6 Hz, 1 H, Ar-H), 6.63 (d, $^4J$ = 2.6 Hz, 1 H, Ar-H), 7.31−7.34 (m, 5 H, Ar-H). − $^{13}$C NMR (75.5 MHz, CDCl$_3$): δ = 19.9 (CH$_3$), 52.0 (OCH$_3$), 55.3 (OCH$_3$), 69.9 (CH$_2$), 92.5 (CH$_2$), 99.1, 108.7, 117.3, 127.8, 128.1, 128.4, 137.0, 138.1, 155.7, 161.1 (CH, C$_q$), 168.7 (C=O).

**(*R*)-5,6-Dihydro-4-hydroxy-6-methyl-2*H*-pyran-2-one [(*R*)-7]:** To a stirred solution of (*R*)-**6**[14] (500 mg, 2.48 mmol) in dry dichloromethane (40 mL) at 0 °C was added trifluoroacetic acid (0.2 mL, 2.48 mmol). After stirring the solution for 24 h at room temperature, the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (PE/acetone/HOAc = 1:1:0.01; $R_f$ = 0.50) to give (*R*)-**7** (247 mg, 78%) as a colorless solid. − M.p. 135 °C. − $[\alpha]_D^{25}$ = −153.80 (*c* = 2.1, EtOH). − $^1$H NMR (300 MHz, CDCl$_3$): δ = 1.50 (d, $^3J$ = 6.3 Hz, 3 H, CH$_3$), 2.35 (dd, $^3J$ = 11.4 Hz, $^2J$ = 18.4 Hz, 1 H, CH$_2$), 2.69 (dd, $^3J$ = 2.6 Hz, $^2J$ = 18.4 Hz, 1 H, CH$_2$), 3.40 (d, $^2J$ = 18.9 Hz, 1 H, CH$_2$, keto form), 3.56 (d, $^2J$ = 18.9 Hz, 1 H, CH$_2$, keto form), 4.79 (m, 1 H, CH). − $^{13}$C NMR (75.5 MHz, CDCl$_3$): δ = 20.4 (CH$_3$), 44.9 (CH$_2$), 46.8 (CH$_2$, keto form), 71.9 (CH), 167.3 (C=O), 200.1 (C=O, keto form). − GC-MS; $R_t$ = 7.13 min, *m*/*z* (%): 128 (37) [M$^+$], 69 (100) [C$_4$H$_5$O$^+$].

**(*S*)-5,6-Dihydro-4-hydroxy-6-methyl-2*H*-pyran-2-one [(*S*)-7]:** The title compound was prepared in 59% yield (556 mg) as a colorless solid, by analogy with the above procedure, starting from (*S*)-**6**[17].

− M.p. 135 °C. − $[\alpha]_D^{25}$ = +145.44 (*c* = 2.1, EtOH). − All other spectral characteristics were identical with those of enantiomer (*R*)-**7**.

**(*R*)-5,6-Dihydro-4-methoxy-6-methyl-2*H*-pyran-2-one [(*R*)-(4)]:** To a stirred suspension of potassium carbonate (373 mg, 2.70 mmol) in dry acetone (10 mL) at room temperature were added (*R*)-5,6-dihydro-4-hydroxy-6-methyl-2*H*-pyran-2-one [(*R*)-**7**] (230 mg, 1.80 mmol) and dimethyl sulfate (0.2 mL, 2.20 mmol). After stirring for 8 h at 56 °C, water was added (50 mL) and the reaction mixture was extracted with dichloromethane (3 × 25 mL). The combined organic layers were dried ($Na_2SO_4$) and the solvent was removed in vacuo. The residue was purified by column chromatography (PE/acetone = 1:1; $R_f$ = 0.43) to give (*R*)-**4** (175 mg, 70%) as a colorless solid − M.p. 61 °C. − $[\alpha]_D^{25}$ = −168.09 (*c* = 1.2, $CHCl_3$). − $^1H$ NMR (300 MHz, $CDCl_3$): δ = 1.41 (d, $^3J$ = 6.3 Hz, 3 H, $CH_3$), 2.32 (dd, $^3J$ = 4.2 Hz, $^2J$ = 17.0 Hz, 1 H, $CH_2$), 2.43 (ddd, $^3J$ = 1.5 Hz, $^3J$ = 11.4 Hz, $^2J$ = 17.0 Hz, 1 H, $CH_2$), 3.71 (s, 3 H, $OCH_3$), 4.50 (m, 1 H, CH), 5.11 (d, $^3J$ = 1.5 Hz, 1 H, =CH). − $^{13}C$ NMR (75.5 MHz, $CDCl_3$): δ = 20.5 ($CH_3$), 34.5 ($CH_2$), 56.0 ($OCH_3$), 72.3 (CH), 90.1 (=CH), 167.5 ($C_q$), 172.8 (C=O). − GCMS; $R_t$ = 8.29 min, *m/z* (%): 142 (100) [$M^+$], 127 (69) [$M^+ - CH_3$], 98 (81) [$M^+ - C_2H_4O$], 68 (95) [$M^+ - C_3H_6O_2$].

**(*S*)-5,6-Dihydro-4-methoxy-6-methyl-2*H*-pyran-2-one [(*S*)-4]:** The title compound was prepared in 74% yield (370 mg) as a colorless solid, by analogy with the above procedure, starting from (*S*)-**7**. − M.p. 61 °C. − $[\alpha]_D^{25}$ = +163.86 (*c* = 1.0, $CHCl_3$). − All other spectral characteristics were identical with those of the enantiomer (*R*)-**4**.

**(*R*)-9-Benzyloxymethoxy-3,4-dihydro-10-hydroxy-7-methoxy-3-methyl-1*H*-naphtho[2,3-c]pyran-1-one [(*R*)-10]:** To a solution of methyl 2-benzyloxymethoxy-4-methoxy-6-methylbenzoate (**3**) (300 mg, 0.95 mmol) in dry THF (5 mL) at −78 °C was added a 2 M solution of LDA (1.0 mL, 1.90 mmol). After stirring the red colored solution for 15 min at −78 °C, a solution of (*R*)-**4** (135 mg, 0.95 mmol) in dry THF (2 mL) was added. The reaction mixture was stirred for 15 min at −78 °C, hydrolyzed with dry ethanol[19] (2 mL) and warmed to room temperature. After addition of aq. $NH_4Cl$ solution (200 mL), the aqueous phase was extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with brine (100 mL) and dried ($Na_2SO_4$). After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography (PE/EE = 3:1; $R_f$ = 0.20) to give (*R*)-**10** (100 mg, 27%) as an orange solid. − M.p. 103 °C. − $[\alpha]_D^{25}$ = −3.17 (*c* = 1.0, $CHCl_3$). − CD (trifluoroethanol): λ (Δε) [nm] = 214 (−5.7), 237 (+1.3), 265 (−4.9). − $^1H$ NMR (300 MHz, $CDCl_3$): δ = 1.52 (d, $^3J$ = 6.3 Hz, 3 H, $CH_3$), 2.96 (m, 2 H, $CH_2$), 3.87 (s, 3 H, $OCH_3$), 4.71 (m, 1 H, CH), 4.84 (s, 2 H, $CH_2$), 5.44 (s, 2 H, $CH_2$), 6.64 (d, $^4J$ = 2.3 Hz, 1 H, Ar-H), 6.65 (d, $^4J$ = 2.3 Hz, 1 H, Ar-H), 6.85 (s, 1 H, Ar-H), 7.29−7.36 (m, 5 H, Ar-H), 13.10 (s, 1 H, OH). − $^{13}C$ NMR (75.5 MHz, $CDCl_3$): δ = 20.7 ($CH_3$), 35.0 ($CH_2$), 55.4 ($OCH_3$), 70.3 ($CH_2$), 75.7 (CH), 93.2 ($CH_2$), 100.6, 100.7, 103.1, 111.3, 115.2, 127.8, 128.1, 128.4, 134.1, 137.0, 141.3, 157.6, 161.5, 164.0 (CH, $C_q$), 171.2 (C=O). − MS; *m/z* (%): 394 (3) [$M^+$], 364 (28) [$M^+ - CH_3O$], 346 (5) [$M^+ - CH_5O_2$], 274 (7) [$M^+ - C_8H_8O$], 91 (100) [$C_7H_7^+$]. − $C_{23}H_{22}O_6$ (394.42): calcd. C 70.04, H 5.62; found C 69.99, H 5.54. − HRMS ($C_{23}H_{22}O_6$): calcd. 394.1416; found 394.1416.

**(*S*)-9-Benzyloxymethoxy-3,4-dihydro-10-hydroxy-7-methoxy-3-methyl-1*H*-naphtho[2,3-c]-pyran-1-one [(*S*)-10]:** The title compound was prepared in 27% yield (100 mg) as an orange solid, by analogy with the above procedure, starting from (*S*)-**4**. − M.p. 103 °C. − $[\alpha]_D^{25}$ = +3.11 (*c* = 1.0, $CHCl_3$). − CD (trifluoroethanol): λ (Δε) [nm] = 215 (+6.4), 238 (−0.8), 264 (+4.6). − All other spectral characteristics were identical with those of the enantiomer (*R*)-**10**.

**(*R*)-3,4-Dihydro-9,10-dihydroxy-7-methoxy-3-methyl-1*H*-naphtho-[2,3-c]pyran-1-one [(*R*)-*semi*-vioxanthin] [(*R*)-2]:** To a solution of (*R*)-**10** (73 mg, 0.19 mmol) in a mixture of ethyl acetate and methanol (2:3 v/v) was added palladium (10%) on charcoal (15 mg). After stirring for two days under hydrogen atmosphere, no more starting material could be detected by TLC. The solvent was evaporated under reduced pressure and the crude product was purified by preparative thin layer chromatography (toluene/EE/HOAc = 50:49:1; $R_f$ = 0.62) to give (*R*)-*semi*-vioxanthin (*R*)-**2** (23 mg, 44%) as an orange solid. − M.p. 176 °C. − CD (trifluoroethanol): λ (Δε) [nm] = 213 (−7.3), 240 (+1.6), 266 (−4.5), 366 (+1.3). − $^1H$ NMR (300 MHz, $CDCl_3$): δ = 1.55 (d, $^3J$ = 6.3 Hz, 3 H, $CH_3$), 2.96 (m, 2 H, $CH_2$), 3.87 (s, 3 H, $OCH_3$), 4.73 (m, 1 H, CH), 6.51 (d, $^4J$ = 2.2 Hz, 1 H, Ar-H), 6.55 (d, $^4J$ = 2.2 Hz, 1 H, Ar-H), 6.87 (s, 1 H, Ar-H), 9.46 (s, 1 H, OH), 13.10 (s, 1 H, OH). − $^{13}C$ NMR (75.5 MHz, $CDCl_3$): δ = 20.8 ($CH_3$), 34.7 ($CH_2$), 55.4 ($OCH_3$), 76.5 (CH), 99.4, 101.5, 109.0, 116.0, 133.1, 140.5, 158.5, 162.9 (CH, $C_q$), 171.5 (C=O). − GCMS; $R_t$ = 14.73 min, *m/z* (%): 274 (100) [$M^+$], 256 (678) [$M^+ - H_2O$], 228 (33) [$M^+ - C_2H_6O$]. − HRMS ($C_{15}H_{14}O_5$): calcd. 274.0845; found 274.0842.

**(*S*)-3,4-Dihydro-9,10-dihydroxy-7-methoxy-3-methyl-1*H*-naphtho-[2,3-c]pyran-1-one [(*S*)-*semi*-vioxanthin] [(*S*)-2]:** The title compound was prepared in 39% yield (17 mg) as an orange solid, by analogy with the above procedure, starting from (*S*)-**10**. − M.p. 176 °C. − CD (trifluoroethanol): λ (Δε) [nm] = 216 (+6.0), 239 (−0.8), 267 (+3.0), 366 (−1.0). − All other spectral characteristics were identical with those of the enantiomer (*R*)-**2**.

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