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ORIGINAL PAPER

# Stereoselective total synthesis of (−)-(5*S*,8*R*,13*S*,16*R*)-pyrenophorol

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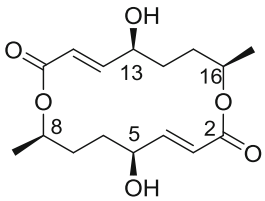
**Abstract** The total synthesis of 16-membered $C_2$-symmetric dilactone (−)-(5*S*,8*R*,13*S*,16*R*)-pyrenophorol was accomplished starting from enantiomerically pure propylene oxide prepared by hydrolytic kinetic resolution of (±)-propylene oxide with key steps of cross-metathesis and intermolecular Mitsunobu cyclization for the construction of macrolactone.

*Graphical abstract*




(–)-(5*S*,8*R*,13*S*,16*R*)-Pyrenophorol

**Keywords** (*S*)-Propylene epoxide · Cross-metathesis reaction · Intermolecular Mitsunobu cyclization · (−)-Pyrenophorol

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## Introduction

Macrodiolides belong to a relatively small but interesting class of natural products, which can be isolated from various fungi and marine sponges, exhibiting many different bioactivities. Macrocyclic dilactones (macrodiolides) are well represented in nature as both homodimers such as pyrenophorol [1–6], pyrenophorin [2, 7], tetrahydropyrenophorol [6], vermiculin [8], and heterodimers including colletodiol [9–12] and grahamimycin A1 [13]. Many of these diolides display strong antifungal [1, 6], anthelmintic [3, 5], and phytotoxic activity [4].

A sixteen-membered diolide, (−)-(5*S*,8*R*,13*S*,16*R*)-pyrenophorol (**1**) was previously isolated from the fungus *Byssochlamys nivea* [1] and subsequently found in *Stemphylium radicinum* [2], *Alternaria alternata* [3], *Drechslera avenae* [4], and *Phoma* sp. [6]. (−)-(5*S*,8*R*,13*S*,16*R*)-pyrenophorol (**1**) exhibits pronounced anthelmintic properties [3, 14] and is moderately active against the fungus *Microbotryum violaceum*. So far **1** has been synthesized by four groups [15–18] due to its interesting structural features combined with biological activity.

The reported synthesis routes to (−)-(5*S*,8*R*,13*S*,16*R*)-pyrenophorol (Fig. 1) are mainly associated with long reaction sequences, low yields, and dependence on the chiral pool resources which are some of the disadvantages in the earlier reported methods. To overcome the problems associated with the earlier approaches, herein we reported an alternative route. In this context, we would like to report an efficient and high yielding enantioselective total synthesis of **1** employing hydrolytic kinetic resolution, cross-metathesis, and intermolecular Mitsunobu cyclization.

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## Results and discussion

Our retro synthetic strategy for the synthesis of **1** is outlined in Scheme 1. We envisioned that the macrodiolide **1** could be obtained from the hydroxy-acid **2** via cyclodimerisation under Mitsunobu conditions followed by deprotection of PMB ethers. Hydroxy-acid **2** could be obtained from ester **6**, which could be prepared from (*S*)-propylene epoxide by Jacobsen hydrolytic resolution of (±)-propylene epoxide.

The synthesis of macrodiolide **1** was initiated from (*S*)-propylene epoxide [19–21] as illustrated in Scheme 2. Accordingly, the epoxide **4** on reaction with allyl magnesium chloride in ether and subsequent silylation of the secondary alcohol **5** with TBSCl and imidazole in $CH_2Cl_2$ gave **6** in 70 % yield. Ozonolysis of **6** in $CH_2Cl_2$ at −78 °C for 30 min gave the corresponding aldehyde, which on subsequent olefination with (ethoxycarbonylmethylene)triphenylphosphorane in $CH_2Cl_2$ at 25 °C for 4 h furnished **3** in 72 % yield. Sharpless asymmetric dihydroxylation [22] of the ester **3** using AD-mix-α in the presence of methanesulfonamide in *t*-BuOH/$H_2O$ (1:1) at 0 °C for 24 h afforded diol **7** in 92 % yield, which was treated with 2,2-dimethoxypropane in the presence of catalytical amounts of PTSA in $CH_2Cl_2$ for 1 h afforded the acetonide **8** in 75 % yield. Reduction of the ester in **8** with DIBAL-H in dry $CH_2Cl_2$ at 0 °C for 1 h gave alcohol **9** in 77 % yield, which was converted into iodide **10** using $I_2$ in the presence of $PPh_3$ and imidazole. Iodide **10**, on reductive fragmentation using Zn powder in ethanol furnished *S*-allylic alcohol **11**, which on treatment with NaH and *p*-methoxybenzyl bromide at 0 °C resulted in the PMB ether **12** in 79 % yield.

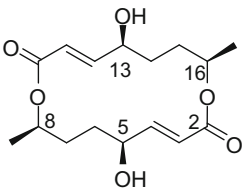
The olefin **12** was subjected to cross-metathesis with ethyl acrylate using Grubb's II catalyst in $CH_2Cl_2$ at reflux temperature for 12 h furnished *trans*-α,β-unsaturated ester **13** in 67 % yield. Ester **13** on subsequent hydrolysis (LiOH in THF:MeOH:$H_2O$ = 3:1:1) afforded acid **14**, which on desilylation with TBAF in dry THF afforded the hydroxy-acid **2** in 82 % yield. Cyclodimerization of hydroxy-acid **2** under Mitsunobu reaction conditions according to Gerlach's procedure [23] with $Ph_3P$ and DEAD at −25 °C for 10 h furnished **15** in 59 % yield. Finally, lactone **15**, on oxidative deprotection of PMB groups using DDQ in aq. $CH_2Cl_2$:$H_2O$ (19:1) provided (−)-(5*S*,8*R*,13*S*,16*R*)-pyrenophorol (**1**) in 81 % yield (Scheme 3). The $^1H$ and $^{13}C$ NMR data and optical rotation value of synthetic **1** were in good agreement with those of the natural product [1].

## Conclusion

In conclusion, the total synthesis of (−)-(5*S*,8*R*,13*S*,16*R*)-pyrenophorol with high enantioselectivity was accomplished in which the stereocenters were established by Jacobsen's hydrolytic kinetic resolution and Sharpless asymmetric dihydroxylation, and cyclization was achieved by intermolecular Mitsunobu cyclization.

## Experimental

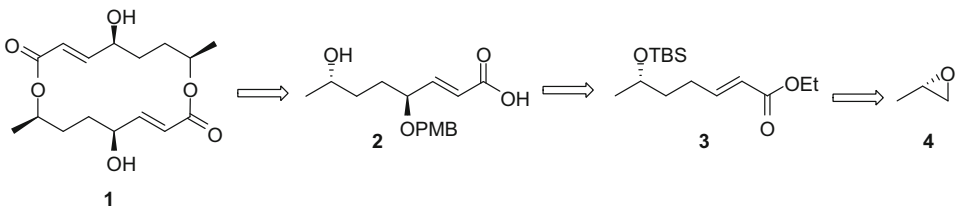
All chemicals and solvents were purchased from Sigma Aldrich and Merck and used without further purification. All reactions were monitored by thin layer chromatography (TLC) on silica Merck 60 F254 percolated aluminum plates. $^1H$ and $^{13}C$ NMR spectra were recorded in 500, 300, 150, and 75 MHz Bruker spectrometers. Chemical shifts are reported in δ units (ppm) with tetramethylsilane (TMS) as a reference. All coupling constants (*J*) are reported in Hertz. Multiplicity is indicated as s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), m (multiplet).



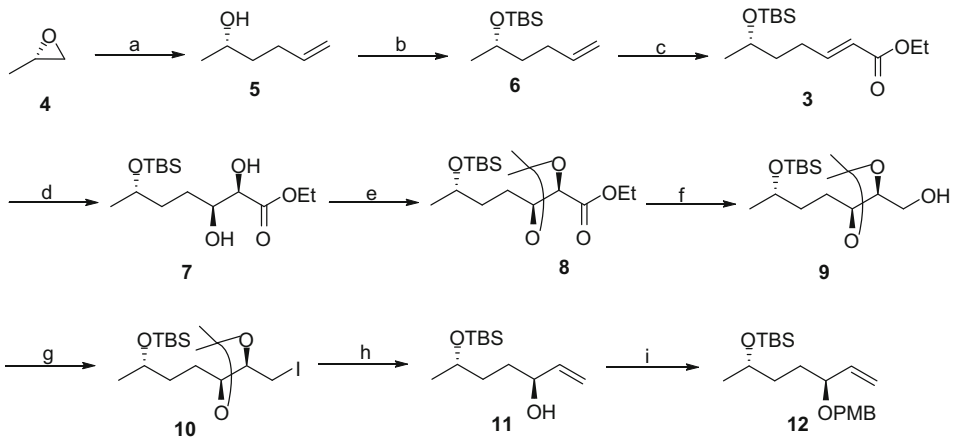

(−)-(5*S*,8*R*,13*S*,16*R*)-Pyrenophorol (**1**)

**Fig. 1** Structure of pyrenophorol

**Scheme 1**

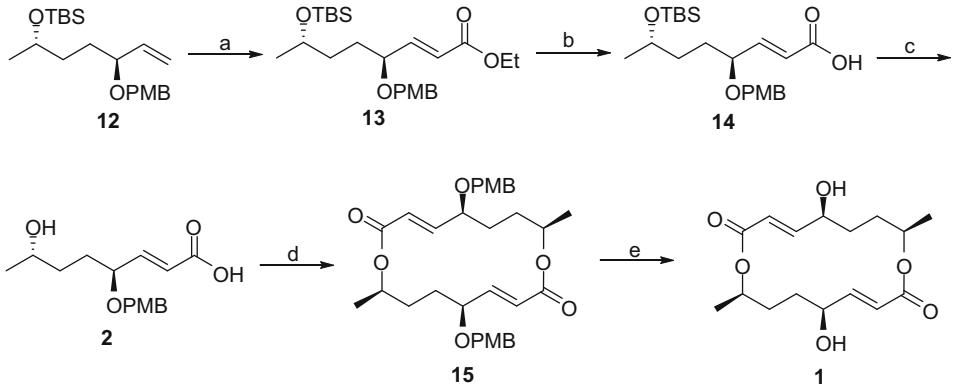


**Scheme 2**




*Reagents and conditions:* (a) allyl chloride, Mg, dry ether, –78 °C, 2 h; (b) TBSCl, Imidazole, $CH_2Cl_2$, 25 °C, 4 h; (c) i) $O_3$, $CH_2Cl_2$, –78 °C, 30 min; ii) Ph3P=CH-$CO_2CH_2CH_3$, $CH_2Cl_2$, 25 °C, 4 h; (d) AD-mix-α, t-BuOH/$H_2O$, 0 °C, 24 h; (e) *p*-TSA, 2,2-DMP, $CH_2Cl_2$, 1.5 h; (f) DIBAL-H, $CH_2Cl_2$, 0 °C to 25 °C, 2 h; (g) $I_2$, imidazole, THF, –40 ºC to 25 °C, 1 h; (h) Zn, EtOH, reflux, 3 h; (i) PMBBr, NaH, THF, 0 °C to 25 °C, 8 h

**Scheme 3**




*Reagents and conditions:* (a) Grubbs-II catalyst (10 mol%), ethyl acrylate, $CH_2Cl_2$, reflux, 12 h; (b) LiOH, THF:MeOH:$H_2O$ (3:1:1), 25 °C, 4 h; (c) TBAF, THF, 0 °C to 25 °C, 3 h; (d) Ph3P, DEAD, toluene: THP (10:1) –25 °C, 10 h; (e) DDQ, $CH_2Cl_2$:$H_2O$ (19:1), 25 °C, 3 h.

FT-IR spectra were taken on IR spectrophotometer using NaCl optics. Mass spectra were performed on direct inlet system or LC by MSD trap SL. Optical rotation values were recorded on digital polarimeter at 25 °C.

*(S)-tert-Butyl(hex-5-en-2-yloxy)dimethylsilane (**6**) [24]*

A suspension of 3.97 g Mg (165.5 mmol, 3.0 eq) and 30 $cm^3$ dry ether was treated with 6.8 $cm^3$ allyl chloride (82.55 mmol, 1.5 eq) at 25 °C and stirred for 30 min. It was cooled to

−78 °C and a solution of 4 $cm^3$ **4** (55.17 mmol, 1.0 eq) in 10 $cm^3$ dry ether was added dropwise and the mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched with 10 $cm^3$ aq. $NH_4Cl$ solution and extracted with ether (2 × 50 $cm^3$). Combined extracts were washed with 30 $cm^3$ brine, dried ($Na_2SO_4$), and concentrated to afford the crude alcohol **5** (5.0 g, 90 %) as a colorless liquid. It is used as such for the next reaction.

A mixture of 5.0 g of the above alcohol **5** (50 mmol, 1.0 eq) and 10.2 g imidazole (150 mmol, 3.0 eq) in 100 $cm^3$ dry $CH_2Cl_2$ was treated with 8.29 g TBSCl (55 mmol, 1.1 eq) at 0 °C under nitrogen atmosphere and stirred at 25 °C for 4 h. The reaction mixture was quenched with 10 $cm^3$ aq. $NH_4Cl$ solution and extracted with $CH_2Cl_2$ (2 × 50 $cm^3$). The combined extracts were washed with 30 $cm^3$ water, 30 $cm^3$ brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by column chromatography (silica gel, 60–120 mesh, *n*-hexane) to furnish **6** (7.5 g, 70 %) as a colorless liquid. $[\alpha]_D^{25} = -57.4°$ ($c = 0.76$, $CHCl_3$).

*(S,E)-Ethyl 6-(tert-butyldimethylsilyloxy)hept-2-enoate (**3**) [24]*

Ozone was bubbled through a cooled (−78 °C) solution of 7.4 g **6** (34.57 mmol, 1.0 eq) in 70 $cm^3$ $CH_2Cl_2$ until the pale blue color persisted. Excess ozone was removed with 2 $cm^3$ $Me_2S$ and stirred for 30 min at 0 °C. The reaction mixture was concentrated under reduced pressure to give the aldehyde, which was used for the further reaction.

To a solution of the above aldehyde in 50 $cm^3$ benzene 18.1 g (ethoxycarbonylmethylene)triphenyl phosphorane (51.86 mmol, 1.5 eq) dissolved in 50 $cm^3$ benzene was added at 0 °C at reflux temperature. After 2 h, solvent was evaporated and the residue purified by column chromatography (silica gel, 60–120 mesh, 8 % EtOAc in pet. ether) afforded **3** (7.6 g, 76 %) as a colorless liquid. $[\alpha]_D^{25} = -21.5°$ ($c = 1.66$, $CHCl_3$).

*(2R,3S,6S)-Ethyl 6-(tert-butyldimethylsilyloxy)-2,3-dihydroxyheptanoate* (**7**, $C_{15}H_{32}O_5Si$)

A mixture of 34.2 g AD-mix-α (24.47 mmol, 1.0 eq) in 60 $cm^3$ of *t*-BuOH/$H_2O$ (1:1 v:v) was stirred at 25 °C for 15 min, and then cooled to 0 °C. To this solution was added 7.0 g ester **3** (24.47 mmol, 1.0 eq). The reaction mixture was stirred at 0 °C for 48 h and then quenched with 7.5 g $Na_2SO_3$ at 0 °C within 0.5 h. EtOAc was added to the reaction mixture, and the aqueous layer was further extracted with EtOAc twice. The combined organic layers were dried over $Na_2SO_4$ and the solvents were evaporated. The crude product was purified by column chromatography (silica gel, 60–120 mesh, 40 % EtOAc in pet. ether) to give corresponding diol **7** (6.4 g, 82 %) as a colorless oil. $[\alpha]_D^{25} = +29.3°$ ($c = 1.18$, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 4.18$ (q, 2H, $J = 7.1$ Hz, –$OCH_2$), 4.06 (m, 2H, 2 –CH), 3.71 (m, 1H, –OCH), 3.09 (br s, 2H, –OH), 1.78–1.66 (m, 2H, –$CH_2$), 1.51–1.39 (m, 2H, –$CH_2$), 1.32 (t, 3H, $J = 7.1$ Hz, –$CH_3$), 1.11 (d, 3H, $J = 6.4$ Hz, –$CH_3$), 0.84 (s, 9H, 3 –$CH_3$), 0.03 (s, 6H, 2 –$CH_3$) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 173.5$, 75.1, 69.8, 68.1, 61.2, 36.6, 32.1, 26.1, 25.2, 18.8, 13.9, −4.9 ppm; IR (neat): $\bar{\nu} = 3{,}384$, 2,930, 1,066, 738, 698 $cm^{-1}$; ESI–MS: $m/z = 343$ ($[M + Na]^+$).

*(4R,5S)-Ethyl 5-[(S)-3-(tert-butyldimethylsilyloxy)butyl]-2,2-dimethyl-1,3-dioxolane-4-carboxylate*

(**8**, $C_{18}H_{36}O_5Si$)

To a cooled (0 °C) solution of 6.1 g **7** (19.06 mmol, 1.0 eq) in 50 $cm^3$ dry $CH_2Cl_2$, 2.8 $cm^3$ 2,2-dimethoxypropane (22.87 mmol, 1.2 eq), and 0.32 g PTSA (1.9 mmol, 0.1 eq) were added and stirred for 1 h. The reaction mixture was neutralized with 5 $cm^3$ $Et_3N$, extracted with $CH_2Cl_2$ (2 × 100 $cm^3$), the organic layers were washed with 50 $cm^3$ water, 25 $cm^3$ brine, dried ($Na_2SO_4$), and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 60–120 mesh, 20 % EtOAc in pet. ether) to furnish **8** (5.5 g, 81 %) as a yellow liquid. $[\alpha]_D^{25} = +56.5°$ ($c = 0.16$, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 4.14$ (q, 2H, $J = 7.2$ Hz, –$OCH_2$), 4.01–3.89 (m, 2H, 2 –CH), 3.82 (m, 1H, –OCH), 1.77–1.60 (m, 2H, –$CH_2$), 1.55 (m, 2H, –$CH_2$), 1.47 (s, 3H, –$CH_3$), 1.44 (s, 3H, –$CH_3$), 1.31 (t, 3H, $J = 7.2$ Hz, –$CH_3$), 1.09 (d, 3H, $J = 6.1$ Hz, –$CH_3$), 0.88 (s, 9H, 3 –$CH_3$), 0.06 (s, 6H, 2 –$CH_3$) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 172.2$, 113.6, 74.6, 74.2, 66.1, 62.2, 36.2, 28.7, 25.8, 24.6, 23.2, 18.8, 13.6, −4.2 ppm; IR (neat): $\bar{\nu} = 2{,}928$, 2,857, 1,612, 1,435, 1,274, 1,078, 699 $cm^{-1}$; ESI–MS: $m/z = 383$ ($[M + Na]^+$).

*[(4S,5S)-5-[(S)-3-(tert-Butyldimethylsilyloxy)butyl]-2,2-dimethyl-1,3-dioxolan-4-yl]methanol* (**9**, $C_{16}H_{34}O_4Si$)

To a stirred solution of 5.4 g ester **8** (14.91 mmol, 1.0 eq) in 30 $cm^3$ dry $CH_2Cl_2$ at −78 °C, 21.2 $cm^3$ DIBAL-H (29.83 mmol, 2.0 eq, 20 mol % in toluene) was added and stirred at the same temperature for 2 h. The reaction mixture was quenched with few drops of MeOH and 5 $cm^3$ aq. sodium potassium tartrate and filtered through Celite. It was dried ($Na_2SO_4$), evaporated, and the residue purified by column chromatography (silica gel, 60–120 mesh, 30 % EtOAc in pet. ether) to give **9** (3.9 g, 83 %) as a colorless liquid. $[\alpha]_D = +130.6°$ ($c = 1.07$, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 4.17$–3.99 (m, 2H, –$OCH_2$), 3.91–3.79 (m, 2H, 2 –CH), 3.78 (m, 1H, –OCH), 1.73–1.62 (m, 2H, –$CH_2$), 1.58 (m, 2H, –$CH_2$), 1.41 (s, 3H, –$CH_3$), 1.38 (s, 3H, –$CH_3$), 1.01 (d, 3H, $J = 6.1$ Hz, –$CH_3$), 0.89 (s, 9H, 3 –$CH_3$), 0.06 (s, 6H, 2 –$CH_3$) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 112.4$, 79.2, 75.8, 66.2, 36.2, 28.4, 26.3, 25.2, 24.3, 18.3, −4.6 ppm; IR (neat): $\bar{\nu} = 3{,}363$, 2,926, 2,856, 1,496, 1,443 $cm^{-1}$; ESI–MS: $m/z = 341$ ($[M + Na]^+$).

*(3S,6S)-6-(tert-Butyldimethylsilyloxy)hept-1-en-3-ol* (**11**, $C_{13}H_{28}O_2Si$)

To a stirred solution of 3.8 g alcohol **9** (11.87 mmol, 1.0 eq) in 50 $cm^3$ dry THF, 1.21 g imidazole (17.80 mmol, 1.5 eq), 3.73 g $Ph_3P$ (14.22 mmol, 1.2 eq), and 3.0 g iodine (11.87 mmol, 1.0 eq) were added at 0 °C. After 1 h the reaction mixture was neutralized by 10 $cm^3$ aq. $NaHCO_3$ solution and extracted with 10 % EtOAc in hexane (2 × 50 $cm^3$). The combined organic layers were washed with 50 $cm^3$ water, 25 $cm^3$ brine, dried ($Na_2SO_4$), and evaporated under reduced pressure. The residue was filtered through a pad of silica (silica gel, 60–120 mesh, 10 % EtOAc in pet. ether) to afford **10** (3.3 g, 66 %) as a yellow colored liquid.

Iodo derivative **10** (3.3 g, 7.83 mmol, 1.0 eq) in 30 $cm^3$ dry ether was immediately treated with 0.72 g sodium metal pieces (31.32 mmol, 4.0 eq) and stirred at 25 °C for 12 h. The reaction mixture was quenched with few drops of MeOH, evaporated and extracted with EtOAc (2 × 50 $cm^3$). It was washed with 20 $cm^3$ water, 20 $cm^3$ brine, dried ($Na_2SO_4$), and evaporated. Purification of the residue by column chromatography (silica gel, 60–120 mesh, 8 % EtOAc in pet. ether) afforded **11** (1.5 g, 77 %) as a colorless oil. $[\alpha]_D^{25} = +75.9°$ ($c = 0.18$, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 5.89$ (m, 1H, olefinic), 5.09 (m, 2H, olefinic), 4.02 (m, 1H, –OCH), 3.83 (m, 1H, –OCH), 1.60–1.34 (m, 4H, 2 –$CH_2$), 1.09 (d, 3H, $J = 5.4$ Hz, –$CH_3$), 0.88 (s, 9H, 3 –$CH_3$), 0.01 (s, 6H, 2 –$CH_3$) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 141.5$, 114.3, 73.3, 68.7, 35.4, 32.7, 26.0, 23.7, 18.0, −4.9, −4.8 ppm; IR (neat): $\overline{\nu} = 3{,}386$, 2,956, 2,857, 1,498, 1,373, 1,253, 1,134, 1,048, 833 $cm^{-1}$; ESI–MS: $m/z = 267$ ($[M + Na]^+$).

*tert-Butyl[(2R,5R)-5-(4-methoxybenzyloxy)hept-6-en-2-yloxy]dimethylsilane* (**12**, $C_{21}H_{36}O_3Si$)

To a cooled (0 °C) solution of 1.4 g **11** (5.73 mmol, 1.0 eq) in 20 $cm^3$ dry THF, 0.41 g NaH (17.21 mmol, 3.0 eq) was added, stirred for 30 min, and treated with a solution of 1.25 g PMBBr (6.30 mmol) in 15 $cm^3$ dry THF. After 7.5 h stirring at room temperature, the reaction mixture was quenched with 10 $cm^3$ sat. $NH_4Cl$ solution and extracted with ethyl acetate (2 × 50 $cm^3$). The organic layers were washed with water (2 × 10 $cm^3$), 10 $cm^3$ brine, and dried ($Na_2SO_4$). Solvent was evaporated under reduced pressure and the residue was purified by column chromatography (silica gel, 60–120 mesh, 5 % EtOAc in pet. ether) to furnish **12** (1.75 g, 85 %) as a yellow liquid. $[\alpha]_D^{25} = +28.6°$ ($c = 1.2$, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 7.19$ (d, 2H, $J = 8.6$ Hz, ArH-PMB), 6.83 (d, 2H, $J = 8.6$ Hz, ArH-PMB), 5.84 (m, 1H, olefinic), 5.19 (m, 2H, olefinic), 4.50, 4.28 (2d, 2H, $J = 11.4$ Hz, –$OCH_2$ Ar), 3.78 (m, 1H, –OCH), 3.66 (s, 3H, –$OCH_3$), 3.62 (m, 1H, –OCH), 1.61–1.28 (m, 4H, 2 –$CH_2$), 1.14 (d, 3H, $J = 6.0$ Hz, –$CH_3$), 0.81 (s, 9H, 3 –$CH_3$), 0.03 (s, 6H, 2 –$CH_3$) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 149.3$, 131.1, 128.2, 128.8, 127.6, 121.0, 72.7, 57.8, 55.3, 35.8, 30.2, 24.9, 23.8, 22.4, -4.3 ppm; IR (neat): $\overline{\nu} = 2{,}932$, 2,863, 1,739, 1,456, 1,268, 1,108 $cm^{-1}$; ESI–MS: $m/z = 387$ ($[M + Na]^+$).

*(4R,7R,E)-Methyl 7-(tert-butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)oct-2- enoate* (**13**, $C_{23}H_{38}O_5Si$)

To a solution of 1.95 g **12** (5.35 mmol, 1.0 eq) in 30 $cm^3$ $CH_2Cl_2$, 0.22 g Grubbs catalyst II (0.26 mmol, 0.05 eq) was added under $N_2$ atmosphere. After heating the solution to reflux, 2.4 g ethyl acrylate (21.41 mmol) dissolved in 8 $cm^3$ dry deoxygenated $CH_2Cl_2$ was added. The mixture was then stirred at reflux for 2 h. After cooling to 25 °C, it was quenched through addition of 0.64 $cm^3$ DMSO (9.0 mmol) followed by stirring overnight. Volatiles were evaporated under reduced pressure and the residue was purified by column chromatography (silica gel, 60–120 mesh, 5 % EtOAc in pet. ether) to furnish **13** (1.55 g, 69 %) as a yellow liquid. $[\alpha]_D^{25} = +46.6°$ ($c = 1.7$, $CHCl_3$); $^1$H NMR ($CDCl_3$, 300 MHz): $\delta = 7.20$ (d, 2H, $J = 8.1$ Hz, ArH-PMB), 6.89 (d, 2H, $J = 8.1$ Hz, ArH-PMB), 6.64 (dd, 1H, $J = 6.3$, 15.6 Hz, olefinic), 5.78 (d, 1H, $J = 15.6$ Hz, olefinic), 4.41 (d, 1H, $J = 11.7$ Hz, benzylic), 4.36 (d, 1H, $J = 11.7$ Hz, benzylic), 3.81 (m, 1H, –OCH), 3.68 (s, 3H, $OCH_3$), 3.59 (s, 3H, $OCH_3$), 3.49 (m, 1H, –OCH), 1.68–1.39 (br m, 4H, 2 –$CH_2$), 1.17 (d, 6H, $J = 6.1$ Hz, –$CH_3$), 0.81 (s, 9H, 3 –$CH_3$), 0.04 (s, 6H, 2 –$CH_3$) ppm; $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta = 167.2$, 158.6, 145.6, 128.1, 123.2, 116.8, 113.3, 79.8, 72.2, 66.6, 53.1, 51.8, 35.8, 30.3, 25.6, 23.3, 18.4, −4.7 ppm; IR (neat): $\overline{\nu} = 2{,}938$, 1,729, 1,608, 1,512, 1,451, 1,379, 1,164, 1,038 $cm^{-1}$; ESI–MS: $m/z = 459$ ($[M + Na]^+$).

*(4R,7R,E)-7-(tert-Butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)oct-2-enoic acid* (**14**, $C_{22}H_{36}O_5Si$)

To a solution of 1.4 g **13** (3.31 mmol, 1.0 eq) in 10 $cm^3$ THF:MeOH:water (3:1:1), 0.24 g LiOH (9.95 mmol) was added and stirred at 25 °C for 4 h. The pH of reaction mixture was adjusted to acidic with 1 N HCl solution and extracted with 20 $cm^3$ ethyl acetate. Organic layers were washed with 10 $cm^3$ water, 10 $cm^3$ brine, dried ($Na_2SO_4$), evaporated under reduced pressure, and purified the residue by column chromatography (silica gel, 60–120 mesh, 35 % EtOAc in pet. ether) to give **14** (1.06 g, 79 %) as a colorless oil. $[\alpha]_D^{25} = +12.6°$ ($c = 0.9$, $CHCl_3$); $^1$H NMR ($CDCl_3$, 300 MHz): $\delta = 7.20$ (d, 2H, $J = 8.0$ Hz, ArH-PMB), 6.86 (dd, 1H, $J = 6.2$, 15.7 Hz, olefinic), 6.83 (d, 2H, $J = 8.0$ Hz, ArH-PMB), 5.71 (d, 1H, $J = 15.7$ Hz, olefinic), 4.41 (d, 1H, $J = 11.5$ Hz, benzylic), 4.27 (d, 1H, $J = 11.5$ Hz, benzylic), 3.83 (m, 1H, –OCH), 3.67 (s, 3H, $OCH_3$), 3.47 (m, 1H, –OCH), 1.67–1.52 (m, 2H, –$CH_2$), 1.49 (m, 2H, –$CH_2$), 1.07 (d, 6H, $J = 6.1$ Hz, –$CH_3$), 0.81

(s, 9H, 3 –$CH_3$), 0.06 (s, 6H, 2 –$CH_3$) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 170.1, 158.4, 149.1, 130.3, 127.9, 117.6, 114.0, 76.1, 73.2, 66.2, 55.7, 38.2, 30.3, 26.3, 24.2, 17.5, -4.3$ ppm; IR (neat): $\overline{\nu} = 3{,}442, 3{,}033, 2{,}930, 2{,}857, 1{,}710, 1{,}097$ cm$^{-1}$; ESI–MS: *m/z* = 431 ($[M + Na]^+$).

*(4R,7R,E)-7-Hydroxy-4-(4-methoxybenzyloxy)oct-2-enoic acid* (**2**, $C_{16}H_{22}O_5$)

To a cooled (0 °C) solution of 1.24 g **14** (3.09 mmol, 1.0 eq) in 15 cm$^3$ dry THF under nitrogen atmosphere, 4.69 cm$^3$ TBAF (4.555 mmol, 1.5 eq) was added and stirred for 3 h. After completion of reaction, reaction mixture was diluted with 5 cm$^3$ water and extracted with ethyl acetate (2 × 40 cm$^3$). Organic layers were washed with water (2 × 10 cm$^3$), 10 cm$^3$ brine, dried ($Na_2SO_4$), evaporated, and the residue was purified by column chromatography (silica gel, 60–120 mesh, 55 % EtOAc in pet. ether) to give **2** (0.89 g, 82 %) as a liquid. $[\alpha]_D^{25} = +35.0°$ ($c = 1.6$, $CHCl_3$); $^1$H NMR ($CDCl_3$, 300 MHz): $\delta = 7.17$ (d, 2H, $J = 8.2$ Hz, ArH-PMB), 6.88 (dd, 1H, $J = 6.1$, 15.8 Hz, olefinic), 6.84 (d, 2H, $J = 8.2$ Hz, ArH-PMB), 5.70 (d, 1H, $J = 15.8$ Hz, olefinic), 4.39 (d, 1H, $J = 11.5$ Hz, benzylic), 4.26 (d, 1H, $J = 11.5$ Hz, benzylic), 4.07–3.89 (m, 1H, –OCH), 3.72 (m, 1H, –OCH), 3.66 (s, 3H, $OCH_3$), 1.67–1.49 (m, 2H, –$CH_2$), 1.47–1.36 (m, 2H, –$CH_2$), 1.07 (d, 6H, $J = 6.0$ Hz, –$CH_3$), 0.81 (s, 9H, 3 –$CH_3$), 0.01 (s, 6H, 2 –$CH_3$) ppm; $^{13}$C NMR ($CDCl_3$, 150 MHz): $\delta = 172.3, 158.1, 146.4, 132.6, 128.1, 119.1, 112.8, 78.9, 70.3, 68.6, 56.2, 34.9, 29.8, 23.6$ ppm; IR (neat): $\overline{\nu} = 3{,}451, 2{,}929, 2{,}857, 2{,}102, 1{,}722, 1{,}612, 1{,}514, 1{,}360, 1{,}041, 777$ cm$^{-1}$; ESI–MS: *m/z* = 317 ($[M + Na]^+$).

*(3E,5R,8S,11E,13R,16S)-5,13-Bis(4-methoxybenzyloxy)-8,16-dimethyl-1,9-dioxacyclo- hexadeca-3,11-diene-2,10-dione* (**15**, $C_{32}H_{40}O_8$)

To a solution of 0.61 g **2** (2.07 mmol, 1.0 eq) and 1.62 g $Ph_3P$ (6.22 mmol, 3.0 eq) in 300 cm$^3$ toluene:THF (10:1) 2.5 cm$^3$ DEAD (16.56 mmol, 8.0 eq) was added at −20 °C and stirred under $N_2$ atmosphere for 10 h. Solvent was evaporated under reduced pressure and the residue was purified by column chromatography (silica gel, 60–120 mesh, 10 % EtOAc in pet. ether) to afford **15** (0.32 g, 57 %) as a colorless oil. $[\alpha]_D^{25} = +18.6°$ ($c = 1.6$, $CHCl_3$); $^1$H NMR ($CDCl_3$, 300 MHz): $\delta = 7.17$ (d, 4H, $J = 8.2$ Hz, ArH-PMB), 6.80 (d, 4H, $J = 8.2$ Hz, ArH-PMB), 6.62 (dd, 2H, $J = 15.9$, 5.3 Hz, olefinic), 5.81 (d, 2H, $J = 15.9$ Hz, olefinic), 5.09–4.96 (m, 2H, 2 -OCH), 4.33 (d, 2H, $J = 11.5$ Hz, benzylic), 4.21 (d, 2H, $J = 11.5$ Hz, benzylic), 4.14 (m, 2H, 2 –OCH), 3.69 (s, 3H, 2 –$OCH_3$) 1.98-1.81 (m, 4H, 2 –$CH_2$), 1.81–1.68 (m, 4H, 2 –$CH_2$), 1.28 (d, 6H, $J = 6.4$ Hz, 2 –$CH_3$) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 166.2, 158.3, 145.2, 129.1, 128.8, 120.2, 113.2, 79.8, 72.2, 66.5, 55.4, 39.3, 28.2, 21.3$ ppm; IR (neat): $\overline{\nu} = 3{,}068, 2{,}932, 2{,}859, 1{,}722, 1{,}608, 1{,}527, 1{,}462, 1{,}427, 1{,}273, 1{,}105, 918, 702$ cm$^{-1}$; ESI–MS: *m/z* = 575 ($[M + Na]^+$).

*(−)-(5S,8R,13S,16R)-Pyrenophorol (**1**)*

To a solution of 131 mg **15** (0.23 mmol, 1.0 eq) in 2 cm$^3$ aq. $CH_2Cl_2$ (19:1), 81 mg DDQ (0.35 mmol, 1.5 eq) was added and stirred at 25 °C for 3 h. The reaction mixture was quenched with 1 cm$^3$ sat. $NaHCO_3$ solution, filtered and washed with 10 cm$^3$ $CH_2Cl_2$. The filtrate was washed with 3 cm$^3$ water, 3 cm$^3$ brine, dried ($Na_2SO_4$), and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 60–120 mesh, 20 % EtOAc in pet. ether) to furnish **1** (61 mg, 83 %) as a white solid. M.p.: 137–138 °C (Ref. [4] 135 °C); $[\alpha]_D^{25} = -4.1°$ ($c = 1.13$, acetone) [Ref. [1] −3.0° ($c = 1.0$, acetone)].

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