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ORIGINAL PAPER

Stereoselective total synthesis of (−)-pyrenophorol

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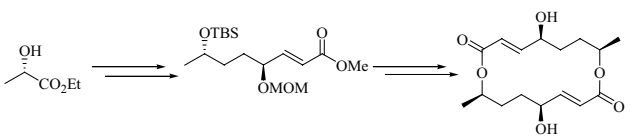
Abstract A simple and efficient stereoselective synthesis of macrodilactone of (−)-pyrenophorol (**1**) has been accomplished in 12 steps in 8.3% overall yield, from inexpensive and commercially available (*S*)-ethyl lactate. This convergent synthesis utilizes an oxidation–reduction protocol and cyclodimerisation under the Mitsunobu reaction conditions as key steps.

Graphical Abstract



Keywords (*S*)-ethyl lactate · Wittig olefination · Intermolecular Mitsunobu cyclization · (−)-Pyrenophorol.

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Introduction

Macrolide molecules are large lactone ring compounds and derived by the internal esterification from the corresponding hydroxy acids (Collins 1999). Macrodiolides and macrocyclic monolactones are two types of macrolides. Researchers across the universe concentrate on the synthesis of both these types of macrocyclic dilactones (Alluraiah et al. 2014; Madala et al. 2016; Ramakrishna et al. 2016; Prataparedy et al. 2017; Ramanujan et al. 2017) and macrocyclic monolactones (Murthy et al. 2014; Prataparedy et al. 2015; Alluraiah et al. 2016).

Macrodiolides belong to one 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 (Kis et al. 1969; Grove 1971; Kind et al. 1996; Kastanias and Chrysayi-Tokousbalides 2000; Ghisalberti et al. 2002; Krohn et al. 2007), pyrenophorin (Nozoe et al. 1965; Grove 1971), tetrahydropyrenophorol (Krohn et al. 2007), vermiculin (Findlay et al. 2003) and heterodimers, it includes colletodiol (Grove et al. 1966; MacMillan and Pryce 1968; Powell and Whalley 1969; MacMillan and Simpson 1973) and grahamimycin A1 (Ronald and Gurusiddaiah 1980). Many of these diolides show strong antifungal (Kis et al. 1969; Krohn et al. 2007), antihelmintic (Kind et al. 1996; Ghisalberti et al. 2002), and phytotoxic activity (Kastanias and Chrysayi-Tokousbalides 2000).

Pyrenophorol (**1**) (Fig. 1) a sixteen-membered diolide, was previously isolated from the fungus *Byssochlamys nivea* (Kis et al. 1969), and subsequently found in *Stemphylium radicinum* (Grove 1971), *Alternaria alternata* (Kind et al. 1996), *Drechslera avenae* (Kastanias and Chrysayi-Tokousbalides 2000) and *Phoma* sp (Krohn et al. 2007).

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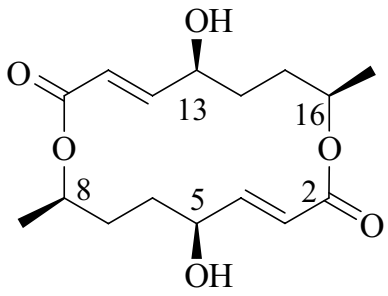


Pyrenophorol (**1**)
(5*S*, 8*R*, 13*S*, 16*R*)

Fig. 1 Structure of (−)-Pyrenophorol

Pyrenophorol (**1**) exhibits pronounced anthelmintic properties (Kind et al. 1996; Christner et al. 1998) and which was moderately active against the fungus *Microbotryum violaceum*. So far pyrenophorol (**1**) has been synthesized by several groups (Dommerholdt et al. 1991; Kibayashi and Machinaga 1993; Yadav et al. 2009; Oh and Kang 2011; Yadav et al. 2012; Edukondalu et al. 2015) due to its interesting structural features combined with its biological activity.

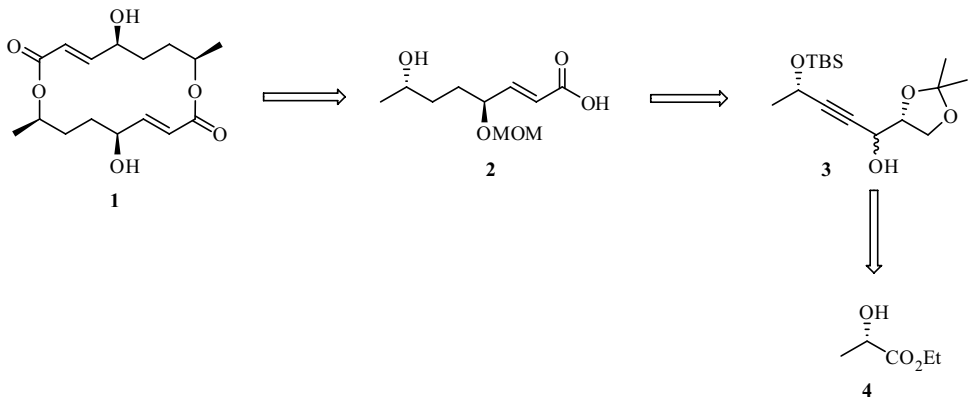
Results and discussion

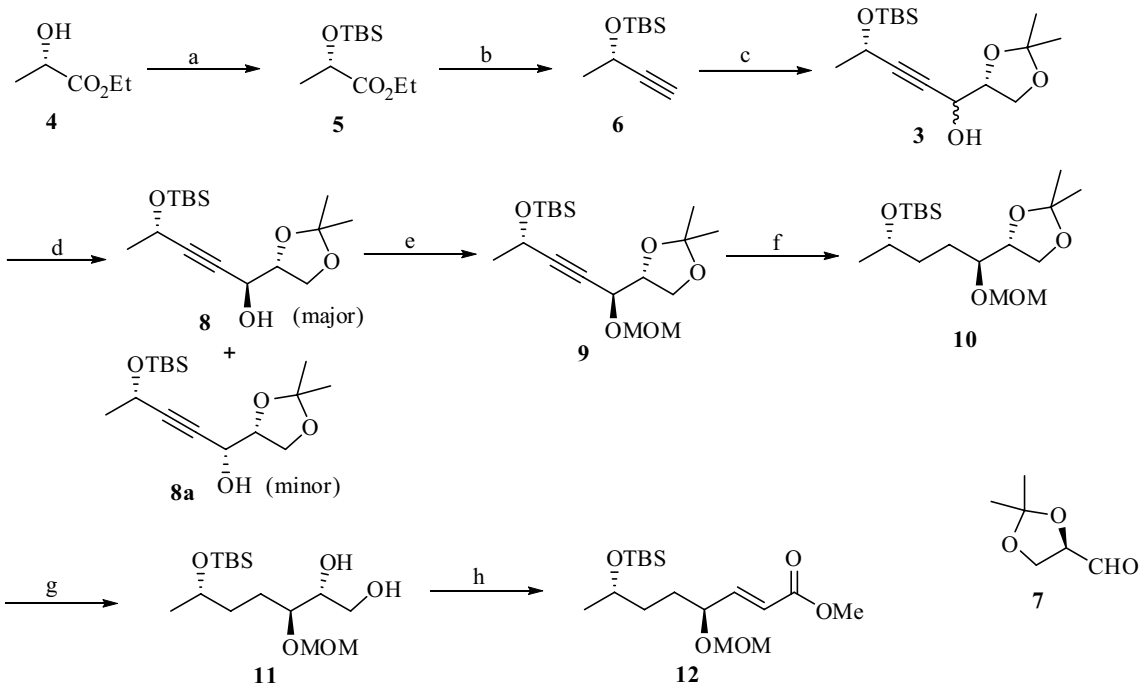
Retrosynthetic analysis of (−)-pyrenophorol (Scheme 1) reveal that it could be obtained from the hydroxy acids **2** via cyclodimerisation under the Mitsunobu conditions followed by deprotection of MOM ether. Hydroxy acid **2** could be prepared from the racemic allylic alcohol **3**, which could be easily prepared from (*S*)-ethyl lactate **4** by simple chemical transformations.

The synthesis of Pyrenophorol (**1**) commenced from commercially available (*S*)-ethyl lactate (**4**) as chiral synthon. Thus, protection of the hydroxyl group with TBSCl and imidazole in CH_2Cl_2 gave ester **5** (Jamieson and Sutherland 2007) in 70% yield. Reduction of ester **5** with DIBAL-H at − 78 °C in dichloromethane to give the corresponding aldehyde, which on treatment with dimethyl(2-oxopropylphosphonate), tosyl azide, K_2CO_3 (acetonitrile, methanol) at 0 °C afforded the known alkyne compound **6** (Brimble and Bryant 2007). The characterization data (^{1}H, ^{13}C NMR) were well matched with the literature value. Alkyne **6** was treated with *n*-BuLi in THF at − 78 °C and the resulting acetylenic anion was quenched with aldehyde **7** [prepared from D-mannitol] (Chatopadyay and Mamdapur 1995), furnished **3** (Scheme 2) in 71% (with 20% de) yield. In order to increase the diastereoselectivity in favor of the requisite stereocenter (anti to the existing one), we reported to an oxidation–reduction protocol. Hence, propargylic alcohol **3** was oxidized with Dess–Martin periodinane in dry CH_2Cl_2 at 0 °C to room temperature for 4 h afforded the corresponding keto compound, which on selective reduction with $Zn(BH_4)_2$ (Takahashi et al. 1985) afforded alcohol **8** and **8a** in 82% (74% de), which were separated by column chromatography. Later, Protection of compound **8** as MOM ether with MOM-Cl in the presence of DIPEA as a base and catalytic amount of DMAP in dry CH_2Cl_2 at 0 °C to room temperature for 6 h gave compound **9** in 91% yield. Reduction of **9** using H_2/Pd–C in MeOH gave **10** in 92% yield. Then acetonide deprotection in compound **10** with aq. 60% acetic acid at room temperature for 12 h afforded the required diol **11** in 74% yield. Oxidative cleavage of diol **11** with $NaIO_4$ and $NaHCO_3$ in CH_2Cl_2 followed by Wittig olefination of the resulting aldehyde afforded **12** in 88% yield.

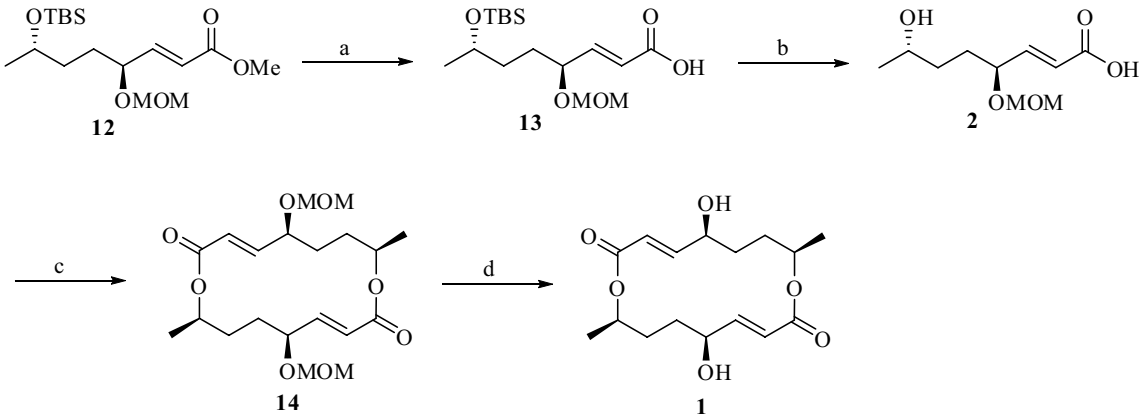
Ester **12** on subsequent hydrolysis (LiOH in THF:MeOH:H_2O-3:1:1) provided acid **13** (Scheme 3), which on desilylation with TBAF in dry THF afforded the hydroxy-acid **2** in 86% yield. Hydroxy-acid **2** on cyclodimerisation under Mitsunobu reaction conditions according to Gerlach's procedure (Gerlach et al. 1977) with Ph_3P and DEAD at − 25 °C for 10 h furnished **14** in 53% yield. Finally, deprotection of MOM group in **14** with 10% HCl in THF for 5 h afforded the (−)-pyrenophorol (**1**) in 77%

Scheme 1 Retrosynthesis of (−)-pyrenophorol





Scheme 2 Reagents and conditions: **a** TBSCl, Imidazole, CH_2Cl_2, rt, 4 h; **b** i) DIBAL-H, CH_2Cl_2, − 78 °C, 1 h; ii) dimethyl(2-oxopropyl) phosphonate, tosyl azide, K_2CO_3, acetonitrile : methanol (2:1), 0 °C-rt, 8 h; **c** *n*-BuLi, dry THF, − 78 °C, **7**, 3 h; **d** i) Dess–Martin periodinane, CH_2Cl_2, 0 °C-rt, 4 h; ii) $Zn(BH_4)_2$, ether, − 30 °C, 3 h; **e** MOMCl, DIPEA, DMAP, CH_2Cl_2, rt, 6 h; **f** 10% Pd/C, H_2, MeOH, 12 h; **g** aq. 60% acetic acid, rt, 12 h; **h** i) $NaIO_4$, sat. $NaHCO_3$ soln., CH_2Cl_2, rt, 5 h; ii) Ph_3P=CHCOOMe, benzene, reflux, 2 h



Scheme 3 Stereoselective total synthesis of (–)-pyrenophorol. Reagents and conditions: **a** LiOH, THF:MeOH:H_2O (3:1:1), rt, 4 h; **b** TBAF, THF, 0 °C to rt, 3 h; **c** Ph_3P, DEAD, toluene:THP (10:1) − 25 °C, 10 h; **d** 10% aq. HCl, THF, 0 °C to rt, 5 h

yield, whose spectral and optical rotation data were comparable with the data reported in the literature (Table 1).

In conclusion, a stereoselective total synthesis of (–)-pyrenophorol was accomplished by a versatile strategy. A combination of oxidation–reduction protocol, Wittig olefination and cyclodimerisation under Mitsunobu reaction condition was effectively utilized in accomplishing the synthesis.

Experimental section

General

Solvents were dried over standard drying agents on freshly distilled prior to use. Chemicals were purchased and used without further purification. All column chromatographic separations were performed using silica gel (60–120 mesh).

Table 1 Comparison of ^{1}H and ^{13}C NMR ($CDCl_3$) data for natural and synthetic Pyrenophorol (**1**) (signals for one half of the symmetric molecule)

No.	Naturally isolated pyrenophorol		Synthesized pyrenophorol	
	^{1}H NMR in δ ppm	^{13}C NMR in δ ppm	^{1}H NMR in δ ppm	^{13}C NMR in δ ppm
1	–	–	–	–
2	–	164.9	–	164.8
3	5.97 (dd, 1H, *J* = 15.7, 1.7 Hz)	122.1	5.95 (d, 1H, *J* = 15.4 Hz)	122.2
4	6.89 (dd, 1H, *J* = 15.7, 5.5 Hz);	149.5	6.88 (dd, 1H, *J* = 15.4, 5.4 Hz)	149.6
5	4.29 (m, 1H)	70.4	4.28–4.19 (m, 1H)	70.3
6	1.88 (m, 2H)	30.4	1.98–1.83 (m, 2H)	30.5
7	1.69 (m, 2H)	28.9	1.77–1.64 (m, 2H)	28.9
8	5.12, m, H	69.7	5.12–5.02 (m, 1H)	69.6
9	1.27 (d, *J* = 6.5 Hz)	18.1	1.26 (d, 3H, *J* = 6.7 Hz)	18.3

Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40 °C in *vacuo*. ^{1}H NMR spectra were acquired at 300 MHz, 500 and 600 MHz, while, ^{13}C NMR at 75 and 125 MHz with TMS as internal standard for solutions in $CDCl_3$. *J* values were given in Hz. IR-spectra were recorded on FT IR spectrophotometer with NaCl optics. Optical rotations were measured on digital polarimeter at 25 °C. Mass spectra were recorded on direct inlet system or LC by MSD trap SL.

(S)-4-(tert-Butyldimethylsilyloxy)-1-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-2-yn-1-ol (3)

To a stirred solution of compound **6** (5.0 g, 27.17 mmol) in dry THF (25 mL), was added n-BuLi (16.8 mL, 40.75 mmol, 2.5 M solution in *n*-hexane) at − 78 °C and stirred for 1 h. A solution of **7** (3.5 g, 27.17 mmol) in dry THF (10 mL) was added at − 78 °C and stirred for 2 h at same temperature. The reaction mixture was quenched with aq. NH_4Cl solution (10 mL) and allowed to stir for 15 min. Organic layer was separated and the aqueous layer washed with ethyl acetate (2 × 20 mL). The combined organic layers were washed with water (2 × 10 mL), brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (60–120 Silica gel, 10% EtOAc in pet. ether) to give **3** (6.1 g, 71%) as a colorless liquid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.36 (m, 1H, –OCH), 4.22 (q, 1H, *J* = 6.6 Hz, $–OCH_2$), 3.92–3.75 (m, 3H, $–OCH_2$, –OCH), 1.37, 1.33 (2 s, 6H, 2 × $–CH_3$), 1.11 (d, 3H, *J* = 6.4, $–CH_3$), 0.91 (s, 9H, *t*-butyl), 0.38 (s, 6H, 2 × $–CH_3$); HRMS (ESI): *m/z* calculated for $C_{16}H_{30}O_4SiNa$ $[M + Na]^+$ 337.1811, found 337.1817.

(1S,4S)-4-(tert-Butyldimethylsilyloxy)-1-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-2-yn-1-ol (8)

To a stirred solution of **3** (5.8 g, 18.47 mmol) in dry CH_2Cl_2 (50 mL), was added Dess-Martin periodinane (11.7 g, 27.7 mmol) at 0 °C and stirred for 4 h at room temperature. The reaction mixture was quenched with 1:1 ratio of sat. $NaHCO_3$ sol. and Hypo sol. (35 mL) and allowed to stirr for 30 min. extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with water (50 mL), dried (Na_2SO_4) and concentrated. The crude residue was purified by column chromatography (60–120 Silica gel, 7% EtOAc in pet. ether) to give corresponding ketone (5.3 g, 92%) as a pale yellow liquid.

To a stirred solution of above obtained ketone (5.2 g, 16.6 mmol) in dry ether (50 mL), was added $Zn(BH_4)_2$ (5.7 mL, 24.9 mmol, 4.4 M solution in *n*-hexane) at − 30 °C and stirred for 3 h The reaction mixture was quenched with aqueous NH_4Cl solution (30 mL) and allowed to stirred for 15 min. Organic layer was separated and the aqueous layer was washed with ethyl acetate (2 × 50 mL). The combined organic layers were washed with water (2 × 50 mL), brine (30 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (60–120 Silica gel, 10% EtOAc in pet. ether) to give **8** (4.2 g, 82% yield) as colorless liquid. $[\alpha]_D$ − 59.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.44 (d, 1H, *J* = 6.4 Hz, –OCH), 4.29 (q, 1H, *J* = 6.4 Hz, –OCH), 3.98-3.78 (m, 3H, $–OCH_2$, –OCH), 1.38, 1.35 (2 s, 6H, 2 × $–CH_3$), 1.07 (d, 3H, *J* = 6.4, $–CH_3$), 0.91 (s, 9H, *t*-butyl), 0.38 (s, 6H, 2 × $–CH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 113.3, 86.3, 83.6, 79.1, 64.2, 63.8, 57.8, 26.1, 24.5, 23.7, 22.1, − 4.1; IR (neat): 750, 890, 1106, 1513, 2932, 3442 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{15}H_{24}O_2S_2Na$ $[M + Na]^+$ 337.1811, found 337.1813.

Spectral data of Minor isomer (**8a**): ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.41 (d, 1H, *J* = 6.1 Hz, –OCH), 4.31–4.26 (m, 1H, –OCH), 4.03-3.90 (m, 2H, $–OCH_2$), 3.84–3.77 (m, 1H, –OCH), 1.37, 1.31 (2 s, 6H, 2 × $–CH_3$), 1.11 (d, 3H, *J* = 6.1, $–CH_3$), 0.94 (s, 9H, *t*-butyl), 0.33 (s, 6H, 2 × $–CH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 113.5, 86.4, 83.7, 78.7, 64.4, 64.1, 57.7, 26.3, 24.4, 23.7, 22.3, − 4.4; ESIMS: 337 $(M + Na)^+$.

(5S,8S)-5-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-8,10,10,11,11-pentamethyl-2,4,9-trioxa-10-siladodec-6-yne (9)

To a cooled (0 °C) solution of **8** (4.1 g, 13.05 mmol) in CH_2Cl_2 (25 mL), were added DIPEA (9.1 mL, 52.2 mmol) and MOM-Cl (2.1 mL, 26.11 mmol) sequentially and stirred at room temperature for 6 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (60–120 Silica gel, 8% EtOAc in pet. ether) to afford **9** (4.5 g, 91%) as a yellow liquid. $[\alpha]_D$ +27.1 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.51, 4.39 (2d, 2H, *J* = 9.4 Hz, –OCH_2), 4.17 (q, 1H, *J* = 5.9 Hz, –OCH), 3.99–3.89 (m, 2H, –OCH_2), 3.76–3.64 (m, 2H, 2 × –OCH), 3.34 (s, 3H, –OCH_3), 1.32, 1.28 (2 s, 6H, 2 × –CH_3), 1.12 (d, 3H, *J* = 6.2 Hz, –CH_3), 0.88 (s, 9H, *t*-butyl), 0.03 (s, 6H, 2 × –CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 107.8, 97.2, 84.3, 79.1, 76.2, 72.1, 63.9, 58.1, 56.0, 25.8, 24.2, 23.1, 21.3, − 4.8; IR (neat): 2929, 2858, 1720, 1609, 1460, 1101, 837 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{18}H_{34}O_5SiNa$ $[M + Na]^+$ 381.2073, found 381.2080.

(5S,8S)-5-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-8,10,10,11,11-pentamethyl-2,4,9-trioxa-10-siladodecane (10)

To a stirred solution of **9** (4.4 g, 12.11 mmol) in EtOAc (20 mL), a catalytic amount of 10% Palladium on carbon (Pd/C) (0.12 g) was added into the reaction mixture and stirred under H_2 atmosphere for 12 h. The reaction mixture was filtered through Celite washed with EtOAc (2 × 20 mL) and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (60–120 Silica gel, 5% EtOAc in pet. ether) to give **10** (4.1 g, 92%) as colorless syrup. $[\alpha]_D^{28}$ = − 37.80 (*c* 1.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.49 (s, 2H, –OCH_2), 3.98-3.79 (m, 3H, -OCH_2, –OCH), 3.54 (m, 1H, –OCH), 3.48 (m, 1H, –OCH), 3.32 (s, 3H, –OCH_3), 1.64–1.51 (m, 4H, 2 × –CH_2), 1.37, 1.33 (2 s, 6H, 2 × –CH_3), 1.09 (d, 3H, *J* = 5.9 Hz, –CH_3), 0.91 (s, 9H, *t*-butyl), 0.37 (s, 6H, 2 × –CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 103.5, 97.1, 83.6, 78.9, 66.2, 64.3, 55.8, 35.1, 28.9, 25.6, 25.4, 24.2, 18.3, − 3.9; HRMS (ESI): *m/z* calculated for $C_{18}H_{38}O_5SiNa$ $[M + Na]^+$ 385.2386, found 385.2394.

(2*R*,3*S*,6*S*)-6-(*tert*-Butyldimethylsilyloxy)-3-(methoxymethoxy)heptane-1,2-diol (11)

A solution of **10** (4 g, 11.04 mmol) in aq. 60% acetic acid (40 mL) was stirred at room temperatature for 12 h. After completion of reaction, it was neutralized with anhydrous $NaHCO_3$ and extracted with ethyl acetate (2 × 100 mL) and dried (Na_2SO_4). Evaporation of solvent under reduced pressure and purification of the residue by column chromatography (60–120 Silica gel, 40% EtOAc in pet. ether) furnished **11** (3.5 g, 74%) as a yellow liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): 4.52 (m, 2H, –OCH_2), 4.08–3.88 (m, 3H, –OCH_2, –OCH), 3.57 (m, 1H, –OCH), 3.43 (m, 1H, –OCH), 3.34 (s, 3H, -OCH_3), 1.74–1.48 (m, 4H, 2 × –CH_2), 1.11 (d, 3H, *J* = 6.0 Hz, –CH_3), 0.92 (s, 9H, *t*-butyl), 0.33 (s, 6H, 2 × –CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 97.1, 83.1, 66.6, 63.8, 56.0, 35.4, 29.0, 25.9, 24.2, 18.3, − 4.1, − 4.6; IR (neat): 3456, 2990, 2942, 2863, 1613, 1513 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{15}H_{35}O_5Si$ $[M + H]^+$ 323.2254, found 323.2259.

(4*S*,7*S*,*E*)-Methyl 7-(*tert*-butyldimethylsilyloxy)-4-(methoxymethoxy)oct-2-enoate (12)

To a cooled (0 °C) solution of **11** (2.5 g, 7.76 mmol) in CH_2Cl_2 (30 mL), were added $NaIO_4$ (2.49 g, 11.64 mmol) followed by sat. $NaHCO_3$ (2 mL) and stirred at room temperature for 5 h. Reaction mixture was dried (Na_2SO_4), filtered and evaporated under reduced pressure to gave corresponding aldehyde, which was directly used as such for the next step.

Aldehyde was dissolved in benzene (30 mL) and treated with (methoxycarbonylmethylene) triphenyl phosphorane (3.2 g, 9.31 mmol) at reflux. After 2 h, solvent was evaporated from reacton mixture and the residue was purified by column chromatography (60–120 Silica gel, 10% EtOAc in pet. ether) to furnish **12** (2.3 g, 88%) as a yellow liquid. $[\alpha]_D$ − 134.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.78 (dd, 1H, *J* = 6.1, 15.6 Hz, olefinic), 5.94 (d, 1H, *J* = 15.6 Hz, olefinic), 4.54 (q, 2H, *J* = 6.7 Hz, –OCH_2), 3.82 (q, 1H, *J* = 5.4, 10.8 Hz, –OCH), 3.68–3.61 (m, 1H, –OCH), 3.59 (s, 3H, –OCH_3), 3.32 (s, 3H, –OCH_3), 1.71–1.38 (m, 4H, 2 × –CH_2), 1.11 (d, 3H, *J* = 6.0 Hz, –CH_3), 0.88 (s, 9H, *t*-butyl), 0.03 (s, 6H, 2 × –CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.9, 149.3, 129.6, 117.2, 96.8, 78.3, 66.9, 56.3, 51.2, 35.9, 31.2, 26.1, 25.9, 24.6, 19.2, − 4.6; IR (neat): 3446, 2932, 1722, 1612, 1512, 1448, 1386, 1164, 1037 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{17}H_{34}O_5SiNa$ $[M + Na]^+$ 369.2073, found 369.2081.

(4*S*,7*S*,*E*)-7-(*tert*-Butyldimethylsilyloxy)-4-(methoxymethoxy)oct-2-enoic acid (13)

To a solution of **12** (1.1 g, 3.17 mmol) in THF: MeOH: water (3:1:1, 10 mL), was added LiOH (0.3 g, 12.7 mmol) and stirred at room temperature for 4 h. The pH of reaction mixture was adjusted to acidic with 1 N HCl solution and extracted with ethyl acetate (20 mL). Organic layers were washed with water (15 mL), brine (15 mL), dried (Na_2SO_4), evaporated under reduced pressure and the residue was

purified by column chromatography (60–120 Silica gel, 30% EtOAc in pet. ether) to give **13** (0.85 g, 81%) as a colourless oil. $[\alpha]_D$ + 14.6 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.74 (dd, 1H, *J* = 5.9, 15.4 Hz, olefinic), 5.97 (d, 1H, *J* = 15.4 Hz, olefinic), 4.51 (s, 2H, –OCH_2), 3.84 (q, 1H, *J* = 5.9, 9.9 Hz, –OCH), 3.68–3.57 (m, 1H, –OCH), 3.39 (s, 3H, –OCH_3), 2.09–1.89 (m, 2H, –CH_2), 1.79–1.68 (m, 2H, –CH_2), 1.13 (d, 3H, *J* = 6.1 Hz, –CH_3), 0.81 (s, 9H, *t*-butyl), 0.01 (s, 6H, 2 × –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7, 152.1, 124.3, 67.9, 67.2, 66.8, 55.2, 35.6, 29.8, 25.3, 18.2, − 4.3; IR (neat): 3540, 3031, 2930, 2857, 1710, 1097 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{16}H_{32}O_5SiNa$ $[M + Na]^+$ 355.1917, found 355.1923.

(4S,7S,E)-7-Hydroxy-4-(methoxymethoxy)oct-2-enoic acid (2)

To a cooled (0 °C) solution of **13** (0.75 g, 2.25 mmol) in dry THF (10 mL) under nitrogen atmosphere, was added TBAF (0.7 mL, 2.7 mmol) and stirred for 3 h. After completion of reaction, reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (2 × 50 mL). Organic layers were washed with water (2 × 10 mL), brine (10 mL), dried (Na_2SO_4), evaporated and the residue was purified by colomn chromatography (60–120 Silica gel, 55% EtOAc in pet. ether) to give **2** (0.42 g, 86%) as a liquid. $[\alpha]_D$ − 32.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.89 (dd, 1H, *J* = 6.3, 15.6 Hz, olefinic), 5.97 (d, 1H, *J* = 15.6 Hz, olefinic), 4.71–4.59 (m, 2H, –OCH_2), 3.74 (q, 1H, *J* = 6.1, 10.4 Hz, –OCH), 3.62–3.54 (m, 1H, –OCH), 3.33 (s, 3H, –OCH_3), 1.95–1.53 (m, 4H, 2 × –CH_2), 1.22 (d, 3H, *J* = 6.3 Hz, –CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.0, 152.4, 121.3, 95.3, 68.0, 67.1, 54.4, 35.1, 27.3, 23.2; IR (neat): 3451, 2929, 2857, 2102, 1722, 1612, 1514, 1360, 1041, 777 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{10}H_{18}O_5Na$ $[M + Na]^+$ 241.1052, found 241.1057.

(3E,5S,8R,11E,13S,16R)-5,13-bis(Methoxymethoxy)-8,16-dimethyl-1,9-dioxacyclohexadeca-3,11-diene-2,10-dione (14)

A solution of **2** (0.24 g, 1.15 mmol) and Ph_3P (1.44 g, 5.55 mmol) in toluene: THF (10:1, 250 mL) was added DEAD (0.96 mL, 5.55 mmol) at − 20 °C and stirred under N_2 atmosphere for 10 h. Solvent was evaporated under reduced pressure from the reaction mixture and the residue was purified by column chromatography (60–120 Silica gel, 10% EtOAc in pet. ether) to afford **14** (0.11 g, 53%) as a colorless oil. $[\alpha]_D$ -15.7 (*c* 1.03, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.63 (dd, 2H, *J* = 6.2, 15.3 Hz, olefinic), 5.82 (d, 2H, *J* = 15.3 Hz, olefinic), 5.11–5.01 (m, 2H, 2 × –OCH), 4.49–4.39 (m, 4H, 2 × –OCH_2), 3.98–3.89 (m, 2H, 2 × –OCH), 3.72 (s, 6H, 2 × –OCH_3), 1.84–1.23 (m, 8H, 4 × –CH_2), 1.11 (d, 6H, *J* = 6.0 Hz, 2 × –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 166.4, 146.9, 123.2, 102.9, 97.3, 79.9, 67.8, 56.6, 39.7, 29.7, 19.6; IR (neat): 3416, 3068, 2932, 2859, 1722, 1608, 1527, 1462, 1427, 1273, 1105, 918, 702 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{20}H_{32}O_8Na$ $[M + Na]^+$ 423.1995, found 423.1992.

Pyrenophorol (1)

To a stirred solution of **14** (75 mg, 0.18 mmol) in THF (2 mL) cooled to 0 °C, was treated with 10% aq. HCl (1 mL) and stirred at room temperature for 5 h. The reaction mixture was quenched with sat. $NaHCO_3$ solution (5 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with water (2 × 10 mL), brine (10 mL), dried (Na_2SO_4), concentrated under reduced pressure and the residue was purified by column chromatography (60–120 Silica gel, 15% EtOAc in pet. ether) to give **1** (45 mg, 77%) as a colourless liquid. m.p.: 137–139 °C; lit. [1] m.p. 135 °C; $[\alpha]_D$ − 3.7 (*c* 0.83, acetone); lit.[1] $[\alpha]_D$ − 3.0 (*c* 1.0, acetone); ^{1}H NMR ($CDCl_3$, 300 MHz): (signals for one half of the symmetric molecule) δ 6.88 (dd, 1H, *J* = 15.4, 5.4 Hz, olefinic), 5.95 (d, 1H, *J* = 15.4 Hz, olefinic), 5.12-5.02 (m, 1H, -OCH), 4.28–4.19 (m, 1H, -OCH), 1.98-1.83 (m, 2H, ×CH2), 1.77×1.64 (m, 2H, × CH2), 1.26 (d, 3H, *J* = 6.7 Hz, ×CH3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.8, 149.6, 122.1, 70.3, 69.6, 30.5, 28.9, 18.3; IR (neat): 3442, 2922, 2853, 1721, 1630, 1126, 835 cm^{-1}; HRMS (ESI): *m/z* calculated for $C_{16}H_{24}O_6Na$ $[M + Na]^+$ 335.1471, found 335.1579.

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