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Research Article

AN ALTERNATIVE TOTAL SYNTHESIS OF (–)-PYRENOPHOROL

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ABSTRACT

Aim: The aim of the present work is to report an alternative strategy to synthesis of (–)-Pyrenophorol. Methods: In this synthesis all intermediates and target compounds were fully characterized by different spectroscopic techniques such as ^{1}H NMR, ^{13}CNMR and EI-MS. Results and Discussion: The total synthesis of 16-membered C_2-symmetric dilactone (–)-Pyrenophorol was prepared from (*R*, *S)*-di epoxide in 9 steps with good yields using Wittig olefination and Mitsunobu cyclization as key steps. Conclusion: A short and efficient stereoselective total synthesis of Pyrenophorol (1) has been achieved from the known di epoxide. The key steps includes Wittig olefination and dimerization by Mitsunobu cyclization.

Keywords: pyrenophorol, Ozonolysis, Wittig olefination, cyclodimerization, Mitsunobu cyclization

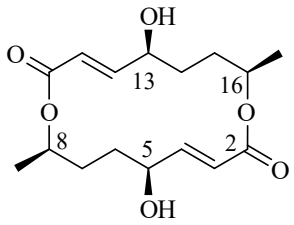
INTRODUCTION

Pyrenophorol (**1**), which belongs to the family of symmetrical macrodiolides, isolated from the fungus *Byssochlamys nivea*[1], and *Stemphylium radicinum*[2]. It was later isolated from *Alternaria alternate*[3], *Drechslera avenae*[4] and *Phoma* sp[5]. Diolide **1** exhibits pronounced anthelmintic properties[3], besides moderate activity against the fungus *Microbotryum violaceum*.

Pyrenophorol (**1**) is a 16-membered bis-lactone embedded with four stereocenters (5S, 8R, 13S, 16R) and two conjugated double bonds. Structurally **1** is related to pyrenophorin[6], and vermiculin[7], while, the monomeric unit, γ-hydroxy-α,β-unsaturated ester is structurally related to 14-membered macrodiolide colletellol[8], Zwanenburg *et al*.[9] reported the synthesis of 5R, 8R, 13R, 16R and 5S, 8R, 13S, 16R isomers of diolide and determined the absolute stereochemistry of **1** as 5S, 8R, 13S, 16R based on the spectral, analytical and optical rotation data.

The structural features coupled with interesting biological activities, prompted several synthesis for **1** by different synthetic strategies[9, 10] while, Floch and Amigoni[11] reported the synthesis of 5R, 8S, 13R, 16S stereisomer. Zwanenburg *et al*.[9] and Kang *et al*.[12] utilized Yamaguchi method[14] for macrolide synthesis, while, Kibayashi *et al*.[10] and Yadav *et al*.[11] adopted dimerization of hydroxy acid under Mitsunobu conditions[15], whereas, Floch, and Amigoni[13] method of macrocyclization was achieved through intramolecular Wittig reaction.

In continuation of our interest on the synthesis of macrodiolides[16-19] herein, we report the synthesis of pyrenophorol (**1**) by adopting dimerization of hydroxy acid using Mitsunobu protocol.



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

Figure 1

MATERIALS AND METHODS

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). 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 MHz and 600 MHz, while, ^{13}C NMR at 75 MHz 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, the HRMS data were obtained using Q-TOF mass spectrometry.

(3*S*,6*S*)-6-(*tert.*-Butyldimethylsilyloxy)hept-1-en-3-ol (3)

To a suspension of trimethylsulfonium iodide (5.70 g, 27.7 mmol) in dry THF (20 mL) at -10 °C under nitrogen atmosphere was added *n*-BuLi (2.5M in hexane, 9.3 mL, 23.3 mmol). After 30 min, compound **6** (3.0 g, 9.3 mmol) in THF (10 mL) was

introduced, producing a milky suspension. The reaction was allowed to warm to 0 ºC over 30 minutes and then to room temperature and stirred for 4 hours. The reaction was quenched with water (20 mL) at 0 ºC, extracted with EtOAc (2 x 50 mL) and the combined organic layers dried over sodium sulfate. The crude residue was purified by column chromatography (60-120 mesh Silica gel) to afford the secondary alcohol **3** (2.2 g) in 70% yield. $[\alpha]_D^{25}$ -37.4 (*c* 0.18, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.81 (m, 1H, olefinic), 5.13 (d, 1H, *J* = 14.8 Hz, olefinic), 5.01 (d, 1H, *J* = 10.4 Hz, olefinic), 3.99 (m, 1H, -CH), 3.78 (m, 1H, -CH), 1.60-1.37 (m, 4H, 2 x -CH_2), 1.06 (d, 3H, *J* = 5.4 Hz, -CH_3), 0.81 (s, 9H, 3 x -CH_3), 0.01 (s, 6H, 2 x -CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.5, 114.3, 72.1, 68.6, 33.1, 26.0, 23.3, 18.0, -4.8, -4.4; IR (neat): 3435, 2929, 2857, 1465, 1373, 1253, 1134, 1048, 833 cm^{-1}; ESIMS *m/z* $(M+Na)^+$:267

(*tert.*-Butyl((2S,5S)-5-(4-methoxybenzyloxy)hept-6-en-2-yloxy)dimethylsilane (7)

To a cooled (0 ºC) solution of **3** (3.0 g, 12.29 mmol) in dry THF (30 mL), NaH (0.59 g, 24.59 mmol) was added, stirred for 30 min and treated with a solution of PMBBr (2.93 g, 14.74 mmol) in dry THF (15 mL). After stirring 7.5 h at room temperature, it was quenched with sat. NH_4Cl solution (10 mL) and extracted with ethyl acetate (2 x 50 mL). Organic layers were washed with water (2 x 10 mL), brine (10 mL) and dried (Na_2SO_4). Solvent was evaporated under reduced pressure and purified the residue by column chromatography (60-120 Silica gel, 5% EtOAc in pet. ether) to furnish **7** (3.7 g, 82%) as a yellow liquid. $[\alpha]_D^{25}$ -23.6 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20 (d, 2H, *J* = 8.6 Hz, ArH-PMB), 6.83 (d, 2H, *J* = 8.6 Hz, ArH-PMB), 5.77-5.61 (heptet, 1H, *J* = 7.5, 10.3 Hz, olefinic), 5.19 (q, 2H, *J* = 4.1, 10.3 Hz, olefinic), 4.54, 4.30 (2d, 2H, *J* = 11.8 Hz, -OCH_2 Ar), 3.78 (s, 3H, -OCH_3), 3.76-3.62 (m, 2H, 2 x -CH), 1.61-1.32 (m, 4H, 2 x -CH_2), 1.20 (d, 3H, *J* = 6.0 Hz, -CH_3), 0.85 (s, 9H, 3 x -CH_3) 0.00 (s, 6H, 2 x -CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.0, 131.5, 128.5, 128.2, 127.6, 121.0, 72.7, 57.80, 55.60, 35.3, 30.2, 25.8, 23.8, 22.4, -4.4; IR (neat): 2926, 2858, 1722, 1456, 1268, 1106 cm^{-1}; ESIMS *m/z* $(M+Na)^+$: 387

(4*S*,7*S*,*E*)-Methyl 7-(*tert.*-butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)oct-2-enoate (8)

Ozone was bubbled through a cooled (-78 °C) solution of **7** (7.4 g, 34.57 mmol) in CH_2Cl_2 (70 mL) until the pale blue color persisted. Excess ozone was removed with Me_2S (2 mL) and stirred for 15 min at 0 °C. The reaction mixture was concentrated under reduced pressure to give aldehyde, which was used for further reaction.

A solution of the above aldehyde in benzene (50 mL) was treated with (methoxy- carbonylmethylene)triphenyl phosphorane (3.54 g, 10.54 mmol) at reflux temperature. After 2 h, solvent was evaporated and purified the residue by column chromatography (60-120 Silica gel, 10% EtOAc in pet. ether) to furnish **8** (3.12 g, 84%) as a yellow liquid. $[\alpha]_D^{25}$ -48.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.16 (d, 2H, *J* = 8.3 Hz, ArH-PMB), 6.81 (d, 2H, *J* = 8.1 Hz, ArH-PMB), 6.77 (dd, 1H, *J* = 6.1, 15.8 Hz, olefinic), 5.94 (d, 1H, *J* = 15.6 Hz, olefinic), 4.47 (d, 1H, *J* = 11.7 Hz, benzylic), 4.24 (d, 1H, *J* = 11.7 Hz, benzylic), 3.87 (q, 1H, *J* = 5.6, 12.1 Hz, -OCH), 3.77 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.61 (m, 1H, -OCH), 1.72-1.31 (br. m, 4H, 2 x -CH_2), 1.07 (d, 3H, *J* = 6.0 Hz, -CH_3), 0.85 (s, 9H, 3 x -CH_3), 0.01 (s, 6H, 2 x -CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 166.5, 158.2, 147.4, 129.7, 128.6, 118.8, 113.5, 79.6, 71.2, 66.6, 55.4, 51.6, 35.4, 30.2, 25.6, 24.2, 18.2, -4.8; IR (neat): 2932, 1724, 1612, 1512, 1448, 1386, 1164, 1037 cm^{-1}; ESIMS *m/z* $(M+Na)^+$: 445

(4*S*,7*S*,*E*)-7-(*tert.*-Butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)oct-2-enoic acid (9)

To a solution of **8** (2.6 g, 6.16 mmol) in THF: MeOH: water (3:1:1, 20 mL), LiOH (0.45 g, 18.48 mmol) was added and stirred at room temperature for 4 h. The pH of reaction mixture was adjusted to acidic with 1N HCl solution and extracted with ethyl acetate (30 mL). Organic layers were washed with water (15 mL), brine (15 mL) and dried (Na_2SO_4). Solvent was evaporated under reduced pressure and purified the residue by column chromatography (60-120 Silica gel, 30% EtOAc in pet. ether) to afford **9** (2.02 g, 80%) as a colourless oil. $[\alpha]_D^{25}$ +14.6 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.19 (d, 2H, *J* = 8.5 Hz, ArH-PMB), 6.94 (dd, 1H, *J* = 6.0, 15.6 Hz, olefinic), 6.81 (d, 2H, *J* = 8.5 Hz, ArH-PMB), 5.91 (d, 1H, *J* = 15.5 Hz, olefinic), 4.48 (d, 1H, *J* = 11.4 Hz, benzylic), 4.29 (d, 1H, *J* = 11.6 Hz, benzylic), 3.90 (q, 1H, *J* = 5.6, 12.1 Hz, -OCH), 3.79 (s, 3H, OCH_3), 3.49 (m, 1H, -OCH), 1.72-1.34 (br. m, 4H, 2 x -CH_2), 1.13 (d, 3H, *J* = 6.0 Hz, -CH_3); 0.85 (s, 9H, 3 x -CH_3), 0.09 (s, 6H, 2 x -CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.8, 158.4, 149.5, 130.6, 128.6, 119.6, 113.5, 78.8, 72.6, 66.6, 55.6, 36.2, 30.8, 25.9, 24.2, 17.6, -4.6; IR (neat): 3540, 3031, 2930, 2857, 1710, 1097 cm^{-1}; ESIMS *m/z* $(M+Na)^+$: 431

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

To a cooled (0 ºC) solution of **9** (2.20 g, 5.40 mmol) in dry THF (15 mL) under nitrogen atmosphere, TBAF (6.5 mL, 6.5 mmol) was added and stirred for 3 h. Reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (2 x 50 mL). Organic layers were washed with water (2 x 10 mL), brine (10 mL) and dried (Na_2SO_4). Solvent was evaporated and purified the residue by colomn chromatography (60-120 Silica gel, 55% EtOAc in pet. ether) to furnish **2** (1.38 g, 87%) as a liquid. $[\alpha]_D^{25}$ -32.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.18 (d, 2H, *J* = 8.6 Hz, ArH-PMB), 6.95 (dd, 1H, *J* = 6.0, 15.6 Hz, olefinic), 6.80 (d, 2H, *J* = 8.6 Hz, ArH-PMB), 5.99 (d, 1H, *J* = 15.6 Hz, olefinic), 4.50 (d, 1H, *J* = 11.6 Hz, benzylic), 4.29 (d, 1H, *J* = 11.6 Hz, benzylic), 3.92 (q, 1H, *J* = 5.6, 12.1 Hz, -OCH), 3.79 (s, 3H, OCH_3), 3.76 (m, 1H, -OCH), 1.72-1.32 (br. m, 4H, 2 x -CH_2), 1.11 (d, 3H, *J* = 6.0 Hz, -CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.6, 158.2, 146.4, 132.6, 128.9, 118.3, 113.6, 78.8, 72.4, 68.2, 56.4, 34.2, 29.8, 23.2; IR (neat): 3451, 2929, 2857, 2102, 1722, 1612, 1514, 1360, 1041, 777 cm^{-1}; ESIMS *m/z* $(M+Na)^+$: 317.1355.

(3*E*,5*S*,8*R*,11*E*,13*S*,16*R*)-5,13-Bis(4-methoxybenzyloxy)-8,16-dimethyl-1,9-dioxacyclo- hexadeca-3,11-diene-2,10-dione (10)

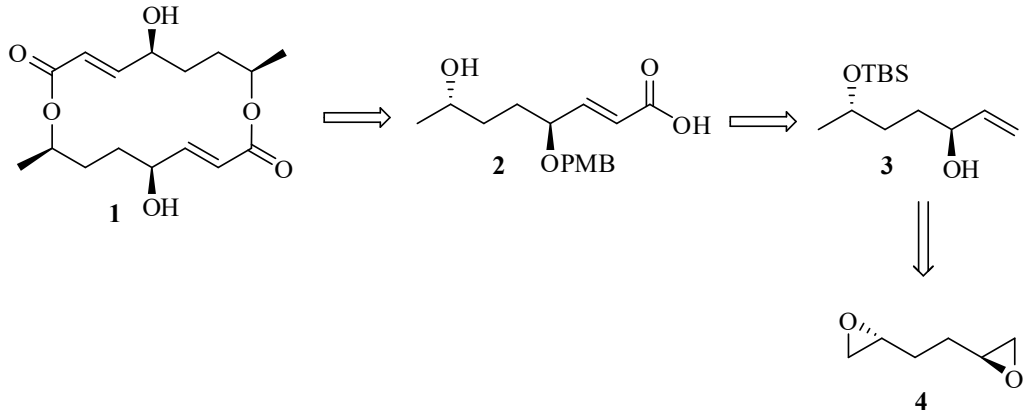
A solution of **2** (0.225 g, 0.93 mmol) and Ph_3P (1.22 g, 4.67 mmol) in toluene: THF (10:1, 250 mL), DEAD (0.81 mL, 16.87 mmol) was added at -20 °C and stirred under N_2 atmosphere for 10 h. Solvent was evaporated under reduced pressure and purified the residue by column chromatography (60-120 Silica gel, 10% EtOAc in pet. ether) to afford **10** (0.14 g, 56%) as a colorless oil. $[\alpha]_D^{25}$ -15.7 (*c* 1.03, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 7.18 (d, 4H, *J* = 8.7 Hz, ArH-PMB), 6.81 (d, 4H, *J* = 8.7 Hz, ArH-PMB), 6.61 (dd, 2H, *J* = 6.2, 11.6 Hz, olefinic), 5.82 (d, 2H, *J* = 11.6 Hz, olefinic), 5.01-4.91 (m, 2H, -OCH), 4.41 (d, 2H, *J* = 11.3 Hz, benzylic), 4.24 (d, 2H, *J* = 11.3 Hz, benzylic), 4.12 (m, 2H, -OCH), 3.61 (s, 6H, OCH_3), 1.79 (q, 4H, *J* = 6.4 Hz, -CH_2), 1.60 (m, 4H, -CH_2), 1.32 (d, 6H, *J* = 7.1 Hz, -CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 166.6, 158.2, 146.2, 129.7, 128.8, 120.6, 113.6, 79.8, 72.4, 68.4, 56.2, 39.6, 28.4, 2.2; IR (neat): 3416, 3068, 2932, 2859, 1722, 1608, 1527, 1462, 1427, 1273, 1105, 918, 702 cm^{-1}; ESIMS *m/z* $(M+Na)^+$: 575

Pyrenophorol (1)

To a solution of **10** (0.12 g, 0.21 mmol) in aq. CH_2Cl_2 (2 mL, 19:1), DDQ (71 mg, 0.31 mmol) was added and stirred at room temperature for 3 h. The reaction mixture was quenched with sat. $NaHCO_3$ solution (1 mL), filtered and washed with CH_2Cl_2 (10 mL). The filtrate was washed with water (3 mL), brine (3 mL) and dried (Na_2SO_4). Solvent was evaporated under reduced pressure and purified the residue by column chromatography (60-120 Silica gel, 20% EtOAc in pet. ether) to furnish **1** (52 mg, 78%) as a white solid. m.p.: 137-139 °C; lit.[1] m.p. 135 °C; $[\alpha]_D$ -3.7 (*c* 0.13, acetone); lit.[1] $[\alpha]_D^{25}$ -3.0 (c 1.0, acetone); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.81 (dd, 2H, *J* = 15.4, 5.1 Hz, olefinic), 5.87 (dd, 2H, *J* = 15.4, 2.0 Hz, olefinic), 5.11-4.99 (m, 2H, 2 x -OCH), 4.21-4.19 (m, 2H, 2 x -OCH), 2.29 (br. s, 2H, 2 x -OH), 2.03-1.93 (m, 4H, 2 x -CH_2), 1.77-1.58 (m, 4H, 2 x -CH_2), 1.23 (d, 6H, *J* = 6.0 Hz, 2 x -CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.5, 143.3, 121.3, 74.1, 68.6, 31.1, 28.9, 19.0; IR (neat): 3442, 2922, 2853, 1721, 1630, 1126, 835 cm^{-1}; ESIMS *m/z* $(M+Na)^+$: 335

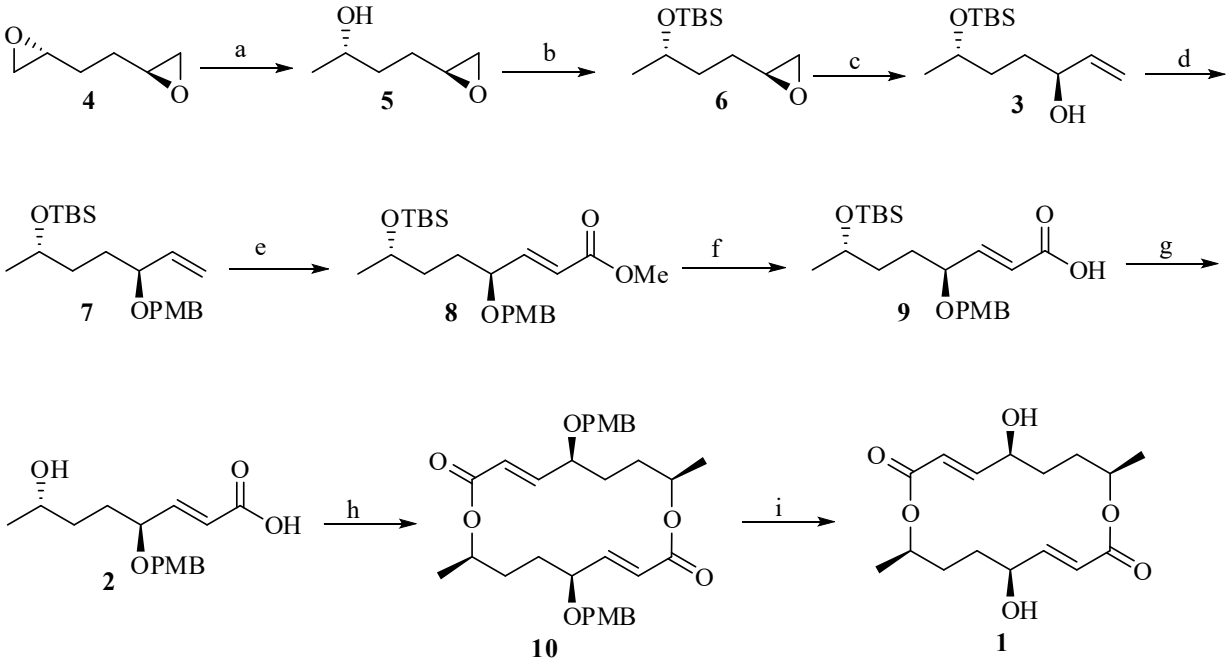
RESULTS AND DISCUSSION

Retrosynthetic analysis of macrodiolide **1** reveal that they could be obtained from the hydroxy acids **2** *via* cyclodimerisation under the Mitsunobu conditions followed by deprotection of PMB ethers. Hydroxy acid **2** could be prepared from the racemic allylic alcohol **3**, which could be prepared from di epoxide **4** by simple chemical transformations.



Scheme 1

The synthesis of macrodiolide **1** was initiated from (*R*, *S*)-di epoxide[20] as illustrated in Scheme 2. Accordingly, the di epoxide **4** was opened regioselectively with DIBAL-H in CH_2Cl_2 at 0 °C to rt and subsequent silylation of the resulting secondary alcohol **5** with TBSCl and imidazole in CH_2Cl_2 gave **6** in 70% yield. Later, the second epoxide ring in compound **6** was also opened with trimethylsulfonium iodide in the presence of *n*-BuLi in THF at -0 °C for 6 h to give the alcohol **3**, which on treatment with NaH and *p*-methoxybenzyl bromide at 0 °C furnished the PMB ether **7** in 82% yield. Next, Ozonolysis of **7** followed by Wittig olefination of the resulting aldehyde afforded **8** in 76% yield.



Scheme 2

Reagents and conditions: (a) DIBAL-H, CH_2Cl_2, 0 °C to rt, 2 h; (b) TBSCl, Imidazole, CH_2Cl_2, rt, 4 h; (c) *n*-BuLi, Me_3SI, THF, 0 °C, 6 h (d) PMBBr, NaH, THF, 0 °C to rt, 8 h; (e) i) O_3, CH_2Cl_2, -78 °C, 30 min; ii) Ph_3P=CHCOOMe, Benzene, reflux, 2 h; (f) LiOH, THF:MeOH:H_2O (3:1:1), rt, 4 h; (g) TBAF, THF, 0 °C to rt, 3 h; (h) Ph_3P, DEAD, toluene:THF (10:1) -25 °C, 10 h; (i) DDQ, CH_2Cl_2:H_2O (19:1), rt, 3 h.

Ester **8** on subsequent hydrolysis (LiOH in THF:MeOH:H_2O-3:1:1) gave acid **9**, which on desilylation with TBAF in dry THF afforded the hydroxy-acid **2** in 87% yield. Hydroxy-acid **2** on cyclodimerization under Mitsunobu reaction conditions according to Gerlach's procedure [13] with Ph_3P and DEAD at -25 °C for 10 h furnished **10**. Finally, oxidative deprotection of PMB groups in **10** using DDQ in aq. CH_2Cl_2:H_2O (19:1) provided (–)-pyrenophorol (**1**) in 78% yield. $[\alpha]_D$ -3.8 (*c* 0.66, acetone); lit.[1,9] $[\alpha]_D$ -3.0 (c 1.0, acetone); The ^1H and ^{13}C NMR data and optical rotation value of synthetic **1** is identical to those reported in the literature.[10]

CONCLUSION

Thus, in summary a short and efficient stereoselective total synthesis of Pyrenophorol (**1**) has been achieved from the known di epoxide. The key steps includes Wittig olefination and dimerization by Mitsunobu cyclization.

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