Chemical Papers
https://doi.org/10.1007/s11696-020-01132-2

ORIGINAL PAPER

Stereoselective total synthesis of (−)-pyrenophorin

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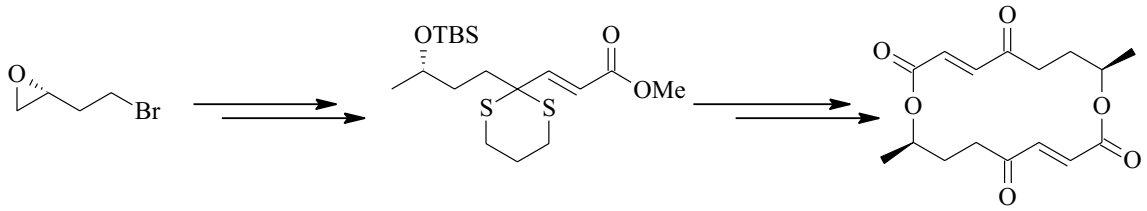
Received: 10 September 2019 / Accepted: 11 March 2020

Abstract
Stereoselective total synthesis of (−)-pyrenophorin was accomplished from commercially available starting material 2-bromo epoxide using regioselective ring opening and the intermolecular Mitsunobu cyclization as key steps.

Graphic abstract



Keywords 2-Bromo epoxide · Regioselective ring opening · Mitsunobu cyclization · (−)-Pyrenophorin

Introduction

Macrodiolides (macrocyclic dilactones) are well represented in nature as both homo- and heterodimers and offer a wide variety of skeletons, ring sizes, and functional groups (Kang and Lee 2005).

Different macrodiolide lactones (Alluraiah et al. 2014; Madala et al. 2016; Prataparedy et al. 2017; Ashok et al. 2018; Edukondalu et al. 2015; Ramakrishna et al. 2016; Ramanujan et al. 2017; Alluraiah et al. 2018; Prataparedy et al. 2019) and macrocyclic monolactones (Alluraiah et al. 2016; Prataparedy et al. 2015; Murthy et al. 2014) were synthesized and reported till date. Natural products with macrodiolide frameworks are also known to exhibit a wide range of biological properties including antibiotic, antifungal (Kis et al. 1969; Krohn et al. 2007; Nozoe et al. 1965), anthelmintic (Kind et al. 1996; Ghisalberti et al. 2002; Christner et al. 1998), phytotoxic (Kastanias and Chrysayi-Tokousbalides 2000, 2005; Sugawara and Strobel 1986), and antileukemic activities. The macrolide dilactone, pyrenophorin, is a good antifungal and herbicidal agent and has been isolated from *Pyrenophora avenae* (Ishibashi 1961), *Stemphylium radicinum* (Grove 1964; Hase et al. 1981), and *Drechslera avenae* (Kastanias and Chrysayi-Tokousbalides 2005). This C_2-symmetric dilactone is derived by head-to-tail dimerization of two identical C8 units. The potent biological activities and interesting structural structural features made an attractive target for the total synthesis of (−)-pyrenophorin (**1**) (Fig. 1), appeared to be an attractive target for total synthesis. A number of synthetic methodologies are reported toward the synthesis of racemic pyrenophorin (Hase et al. 1981; Asaoka and Takei 1981; Fujisawa et al. 1982; Wakamatsu et al. 1985) and optically active pyrenophorin (Steliou and Poupart 1983; Hatakeyama et al. 1987; Baldwin et al. 1992; Kobayashi et al. 1998; Furstner et al. 2001).

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11696-020-01132-2) contains supplementary material, which is available to authorized users.

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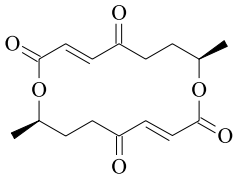
Published online: 16 March 2020

Fig. 1 Structure of (−)-pyrenophorin (**1**)

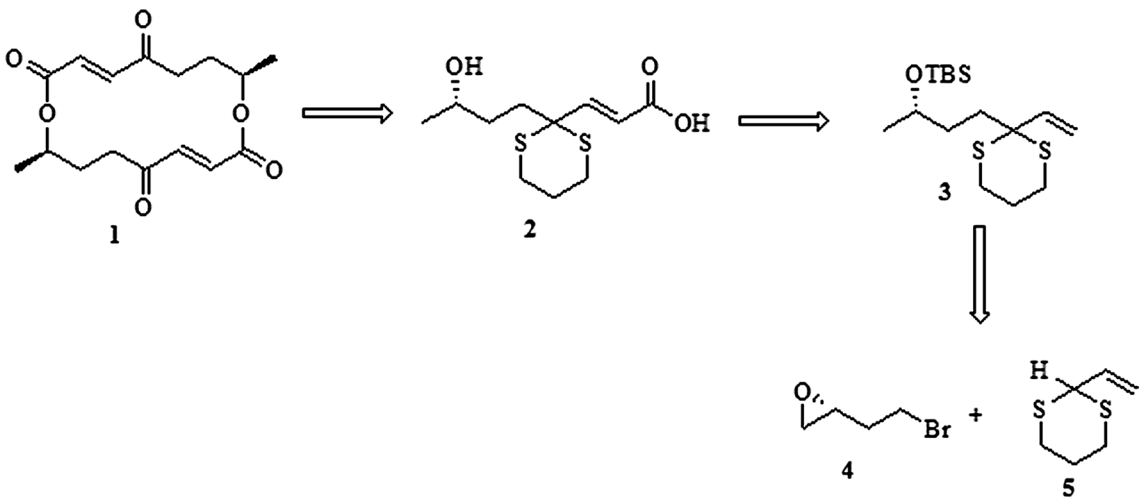


Seuring and Seebach reported this synthesis through Mitsunobu reaction followed by hydrolysis of thioketal diolides with mercuric oxide or boron trifluoride (Seuring and Seebach 1978). The reported above methods are associated with hard reaction conditions, lower yields, and chiral pool resources. To overcome the problems associated with the above methods, herein, we reported another alternative synthetic route in an entirely different strategy. This methodology involves the synthesis of **1** from inexpensive starting material, i.e., 2-bromoethyloxirane and subsequent regioselective ring opening and the intermolecular Mitsunobu cyclization.

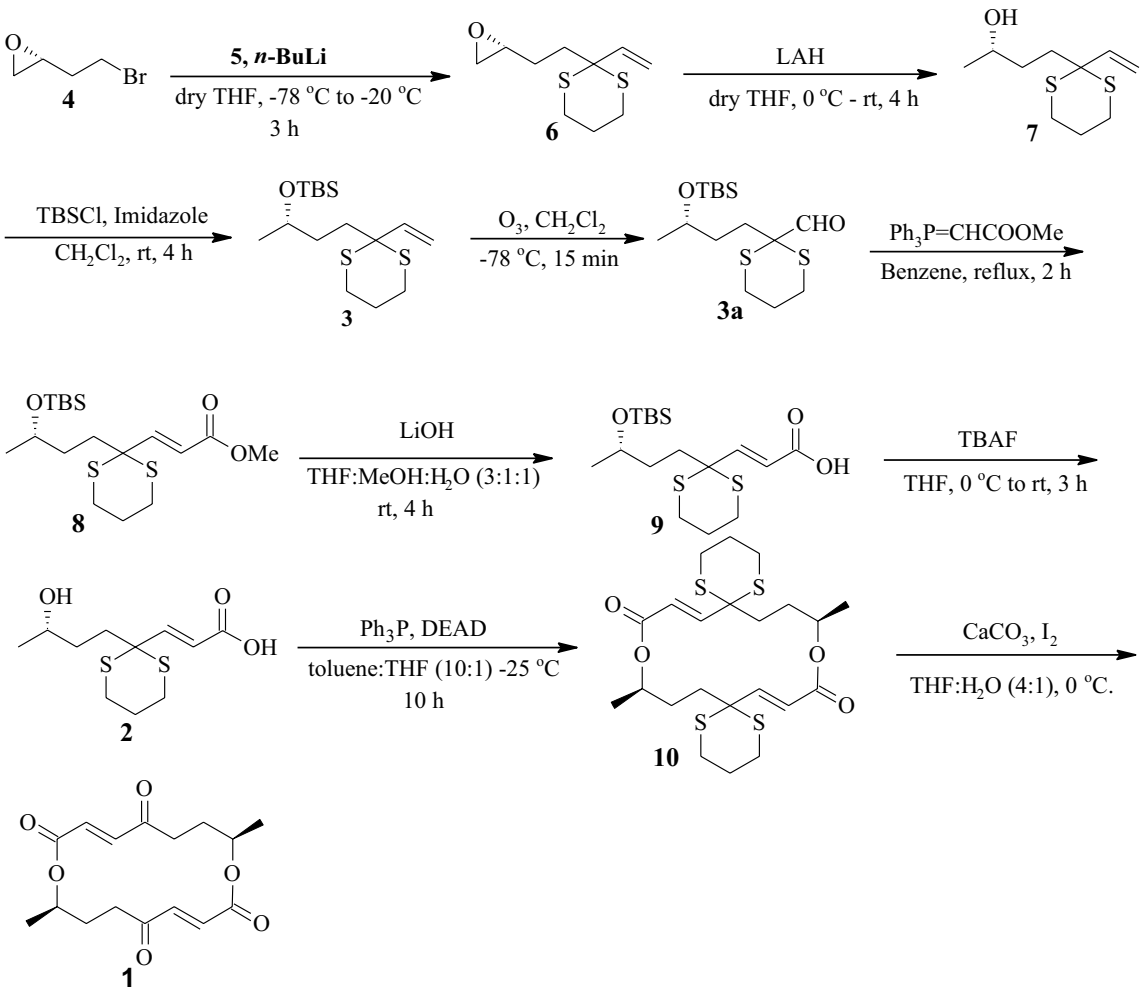
Results and discussion

The retrosynthetic analysis of **1** is shown in Scheme 1. The macrolide **1** could be obtained from the hydroxy acid **2** via cyclodimerization under the Mitsunobu reaction conditions followed by a deprotection of 1,3-dithiane. Hydroxy acid could be achieved from olefin **3**, while the olefin **3** could be prepared by the coupling of 2-vinyl-1,3-dithiane **5** with bromo epoxide **4**.

The stereoselective total synthesis of (−)-pyrenophorin is shown in Scheme 2. From the retrosynthesis, the known 2-bromoethyloxirane **4** (Larson et al. 2011) on alkylation with 2-vinyl-1,3-dithiane **5** in dry THF gave compound **6** in 75% yield. Later, epoxide in **6** was opened regioselectively with LAH in dry THF at 0 °C to room temperature for 4 h that leads to a regioselective opening of epoxide to provide **7** in 83% yield. Alcohol obtained in the above step was silylated using TBSCl in the presence of imidazole in CH_2Cl_2 at room temperature for 4 h to afford compound **3** in 82% yield. Olefin **3** was subjected to ozonolysis in CH_2Cl_2 at − 78 °C for 15 min to give the corresponding aldehyde **3a**, which on immediate treatment with (methoxycarbonylmethylene)triphenylphosphorane in benzene at reflux for 2 h furnished exclusively *trans*-Wittig product **8** in 86% yield. Next, hydrolysis of ester **8** using LiOH in THF/MeOH/water (3:1:1, 20 mL) at room temperature for 4 h afforded acid **9** in 79% yield. Further, desilylation in **9** with TBAF in dry THF at 0 °C to room temperature for 4 h afforded the hydroxy acid **2** in 86% yield. Having completed hydroxy acid **2**, it was aimed to cyclodimerization under the Mitsunobu conditions according to Gerlach's procedure (Gerlach et al. 1977). Thus, a reasonably dilute solution of hydroxy acid **2** in toluene–THF (10:1) was treated with Ph_3P and DEAD at − 25 °C for 10 h. The cyclodimerization took place with complete inversion of chirality at C-7 to furnish **10** in 61% yield. Finally, deprotection of 1,3-dithiane group in compound **10** with $CaCO_3$ and I_2, in THF/H_2O for 20 min, afforded the pyrenophorin **1** in 73% yield as a white solid. m.p. 171–173 °C (lit. (Nozoe et al. 1965) m.p. 175 °C); $[\alpha]_D$ − 57.3 (c 0.65, acetone) [lit. (Seebach et al. 1977) $[\alpha]_D$ − 54.5 (c 0.48, acetone)]. The ^1H and ^{13}C NMR data and optical rotation value of synthetic **1** were in good accordance with data reported in the literature (Zhang et al. 2008).



Scheme 1 Retrosynthetic analysis of (−)-pyrenophorin



Scheme 2 Stereoselective total synthesis of (−)-pyrenophorin

Experimental section

General

All the chemical reagents and solvents were supplied by Sigma-Aldrich and AVRA, India. The solvents were further purified by using basic purification techniques. The progress of the chemical reactions was monitored by TLC plates supplied by Merck Company. ^{1}H and ^{13}C NMR spectra were recorded on Bruker spectrometer at 300 and 150/75 MHz, respectively. Chemical shifts and coupling constants are reported in δ units and Hertz, respectively. Different multiplicities such as singlet, doublet, double doublet, triplet, quadruplet, and multiplet were indicated by s, d, dd, t, q, and m. Mass values are noted as ESIMS. A digital polarimeter was used to measure the optical rotation values at 25 °C.

(R)-2-(2-(2-Vinyl-1,3-dithian-2-yl)ethyl)oxirane (6)

To a stirred solution of 2-vinyl dithiane (4.7 g, 32.22 mmol) in dry THF (30 mL) cooled at − 78 °C was added a 1.6 M solution of n-BuLi in hexane (21.8 mL, 34.86 mmol) dropwise. The reaction mixture was stirred at − 20 °C for 1.5 h. After cooling to − 78 °C, a solution of bromide **4** (4.0 g, 26.84 mmol) in THF (10 mL) was added dropwise, and the mixture was kept at − 30 °C for 2 h. The reaction was quenched with water (30 mL), and the mixture was extracted with Et_2O (2 × 50 mL). The combined extracts were washed with brine (30 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel chromatography (60–120 silica gel, 10% EtOAc in pet. ether) to give **6** (4.27 g, 75%) as a colorless oil. ^{1}HNMR (200 MHz, $CDCl_3$): δ 5.84 (m, 1H), 5.01–4.93 (m, 2H), 3.01–2.90 (m, 1H), 2.83–2.70 (m, 4H), 2.66 (dd, 1H, J = 2.7,

5.1 Hz), 2.44 (dd, 1H, $J = 2.7$, 4.9 Hz), 2.04–1.88 (m, 2H), 1.73–1.61 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2, 121.3, 65.1, 55.9, 46.3, 37.3, 30.1, 27.3, 24.6; ESIMS: 239 $(M + Na)^+$.

(S)-4-(2-Vinyl-1,3-dithian-2-yl)butan-2-ol (7)

To a stirred suspension of LAH (0.68 g, 28.47 mmol) in dry THF (5 mL), a solution of **6** (4.1 g, 18.98 mmol) in dry THF (10 mL) was added dropwise at 0 °C under a nitrogen atmosphere and the mixture was stirred for 4 h at room temperature. The reaction mixture was cooled to 0 °C, treated with saturated aq. Na_2SO_4 solution, and filtered, and the filtrate was dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (60–120 silica gel, 18% EtOAc in pet. ether) to give **7** (3.42 g, 83%) as a colorless syrup. $[\alpha]_D$ + 28.1 (*c* 0.49, $CHCl_3$); ^{1}HNMR (200 MHz, $CDCl_3$): δ 5.79 (m, 1H), 4.99–4.87 (m, 2H), 3.72–3.60 (m, 1H), 2.91–2.80 (m, 4H), 2.26 (brs, 1H), 1.94–1.77 (m, 2H), 1.73–1.57 (m, 4H), 1.11 (d, 3H, $J = 6.0$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.9, 120.8, 71.3, 55.8, 36.9, 34.3, 27.2, 24.2, 23.3; ESIMS: 219 $(M + H)^+$.

(S)-tert-Butyldimethyl(4-(2-vinyl-1,3-dithian-2-yl) butan-2-yloxy)silane (3)

A mixture of the above alcohol **7** (3.2 g, 14.67 mmol) and imidazole (2.99 g, 44.03 mmol) in dry CH_2Cl_2 (50 mL) was treated with TBSCl (2.40 g, 16.06 mmol) at 0 °C under a nitrogen atmosphere and stirred at room temperature for 4 h. The reaction mixture was quenched with aq. NH_4Cl solution (30 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined extracts were washed with water (30 mL) and brine (30 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (60–120 silica gel, 5% EtOAc in pet. ether) to furnish **3** (3.99 g, 82%) as a colorless liquid. $[\alpha]_D$ + 82.6 (*c* 0.55, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.87 (m, 1H), 5.11–4.92 (m, 2H), 3.77–3.62 (m, 1H), 2.87–2.73 (m, 4H), 1.95–1.80 (m, 3H), 1.72–1.61 (m, 3H), 1.12 (d, 3H, $J = 6.2$ Hz), 0.87 (s, 9H), 0.19 (s, 3H), 0.06 (s, 3H);^{13}C NMR (75 MHz, $CDCl_3$): δ 136.4, 120.7, 72.1, 55.8, 38.3, 35.9, 27.3, 26.0, 24.1, 23.8, 18.3, −4.2, −4.7; ESIMS: 355 $(M + Na)^+$, 333 $(M + H)^+$.

(S, E)-Methyl 3-(2-(3-(tert-butyldimethylsilyloxy) butyl)-1,3-dithian-2-yl)acrylate (8)

Ozone was bubbled through a cooled (−78 °C) solution of **3** (3.6 g, 10.84 mmol) in CH_2Cl_2 (40 mL) until the pale blue color persisted. Excess ozone was removed with Me_2S (4 mL) and stirred for 15 min at 0 °C. The reaction mixture was concentrated under reduced pressure to give aldehyde **3a**, which was used for further reaction.

Solution of the above aldehyde **3a** in benzene (50 mL) was treated with (methoxycarbonylmethylene)triphenylphosphorane (4.52 g, 13.03 mmol) at reflux temperature. After 2 h, solvent was evaporated and the residue was purified by column chromatography (60–120 silica gel, 10% EtOAc in pet. ether) to furnish **8** (3.62 g, 86%) as a yellow liquid.$[\alpha]_D$ −48.6 (*c* 1.0, $CHCl_3$); ^{1}HNMR (200 MHz, $CDCl_3$): δ 6.96 (d, 1H, $J = 15.2$ Hz), 6.19 (d, 1H, $J = 15.2$ Hz), 3.86–3.74 (m, 1H), 3.73 (s, 3H), 2.97–2.72 (m, 4H), 2.12–1.57 (m, 6H), 1.12 (d, 3H, $J = 6.3$ Hz), 0.89 (s, 9H), 0.26 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 150.3, 122.8, 69.3, 53.9, 40.1, 37.3, 33.4, 27.2, 25.9, 24.8, 23.8, 18.2, −4.3, −4.6; ESIMS: 413 $(M + Na)^+$.

(S, E)-3-(2-(3-(tert-Butyldimethylsilyloxy) butyl)-1,3-dithian-2-yl)acrylic acid (9)

To a solution of **8** (1.5 g, 3.84 mmol) in THF/MeOH/water (3:1:1, 20 mL), LiOH (0.27 g, 11.53 mmol) was added 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 (30 mL). Organic layers were washed with water (15 mL) and brine (15 mL), dried (Na_2SO_4), and evaporated under reduced pressure, and the residue was purified by column chromatography (60–120 silica gel, 30% EtOAc in pet. ether) to give **9** (1.14 g, 79%) as a colorless oil. $[\alpha]_D$ + 14.6 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.03 (d, 1H, $J = 15.6$ Hz), 6.22 (d, 1H, $J = 15.6$ Hz), 3.80–3.72 (m, 1H), 2.92–2.80 (m, 4H), 2.06–1.88 (m, 3H), 1.81–1.64 (m, 3H), 1.11 (d, 3H, $J = 6.0$ Hz), 0.88 (s, 9H), 0.22 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 152.6, 122.7, 68.7, 53.0, 37.3, 33.7, 27.1, 25.9, 23.8, 18.2, −4.4, −4.6; ESIMS: 399 $(M + Na)^+$.

(S, E)-3-(2-(3-Hydroxybutyl)-1,3-dithian-2-yl)acrylic acid (2)

To a cooled (0 °C) solution of **9** (1.0 g, 2.65 mmol) in dry THF (10 mL) under nitrogen atmosphere, TBAF (3.9 mL, 3.98 mmol) was added 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) and brine (10 mL), dried (Na_2SO_4), and evaporated, and the residue was purified by column chromatography (60–120 silica gel, 55% EtOAc in pet. ether) to give **2** (0.59 g, 86%) as a liquid. $[\alpha]_D$ −62.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.01 (d, 1H, $J = 15.8$ Hz), 6.19 (d, 1H, $J = 15.8$ Hz), 3.91–3.79 (m, 1H), 2.91–2.76 (m, 4H), 1.99–1.83 (m, 2H), 1.71–1.53 (m, 4H), 1.21 (d, 3H, $J = 6.1$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ171.0, 152.1, 123.1, 68.3, 53.2, 37.3, 33.4, 27.2, 25.3, 23.4; ESIMS: 285 $(M + Na)^+$.

Macrodilactone (10)

A solution of **2** (0.5 g, 1.90 mmol) and Ph_3P (2.49 g, 9.54 mmol) in toluene/THF (10:1, 750 mL) DEAD (3.6 mL, 34.21 mmol) was added at − 25 °C and stirred under N_2 atmosphere for 10 h. Solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (60–120 silica gel, 10% EtOAc in pet. ether) to afford **10** (0.28 g, 61%) as a colorless oil. $[\alpha]_D$-15.7 (*c*1.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.81 (d, 2H, $J = 15.1$ Hz), 6.20 (d, 2H, $J = 15.1$ Hz), 5.20–5.09 (m, 2H), 3.03–2.82 (m, 8H), 2.02–1.61 (m, 12H), 1.21 (d, 6H, $J = 6.1$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 149.2, 124.7, 69.0, 53.2, 34.7, 28.1, 26.9, 25.2, 18.1; ESIMS: 489 $(M+H)^{+\cdot}$

Pyrenophorin (1)

To a solution of compound **10** (0.2 g, 0.40 mmol) and $CaCO_3$ (0.40 g, 4.09 mmol) in THF/H_2O (v/v, 4:1, 10 mL) was added I_2 (0.30 mg, 1.22 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 20 min. The reaction was quenched by adding saturated aqueous $Na_2S_2O_3$, filtered through a pad of Celite, then extracted with EtOAc (3 × 20 mL), water, and brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography on silica gel (60–120 silica gel, 15% EtOAc in pet. ether) gave compound **1** (92 mg, 73% yield: $[\alpha]_D$ − 57.3 (c 0.65, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.94 (d, 2H, $J = 16.1$ Hz), 6.48 (d, 2H, $J = 16.1$ Hz), 5.03 (m, 2 H), 2.67 (ddd, 2H, $J = 14.1$, 8.7, 3.8 Hz), 2.54 (ddd, 2H, $J = 14.1$, 8.2, 3.8 Hz), 2.14 (m, 2 H), 2.08 (m, 2 H), 1.27 (d, 6H, $J = 6.4$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.4, 164.7, 139.7, 131.3, 72.1, 37.4, 32.1, 19.7; ESIMS: 309 $(M+H)^+$.

Conclusion

The stereoselective synthesis of pyrenophorin **1** was achieved from known 2-bromoethyloxirane using regioselective ring opening and the intermolecular Mitsunobu cyclization as key steps by overcoming the less yield and hard reaction conditions of earlier reported methods.

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