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Total Synthesis of (-)-Pyrenophorin

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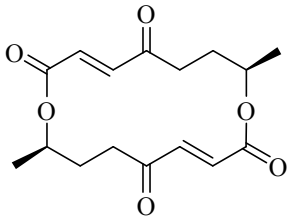
Abstract: In this communication, a simple route for the synthesis of (-)-pyrenophorin in enantioselcetive way, has been described. To accomplish this target, Regioselective ring opening and Mitsunobu cyclodimerisation have been applied as key transformations.

Key words: 2-vinyl-1,3-dithiane, Regioselective ring opening, Wittig olefination, Mitsunobu reaction.

Introduction:

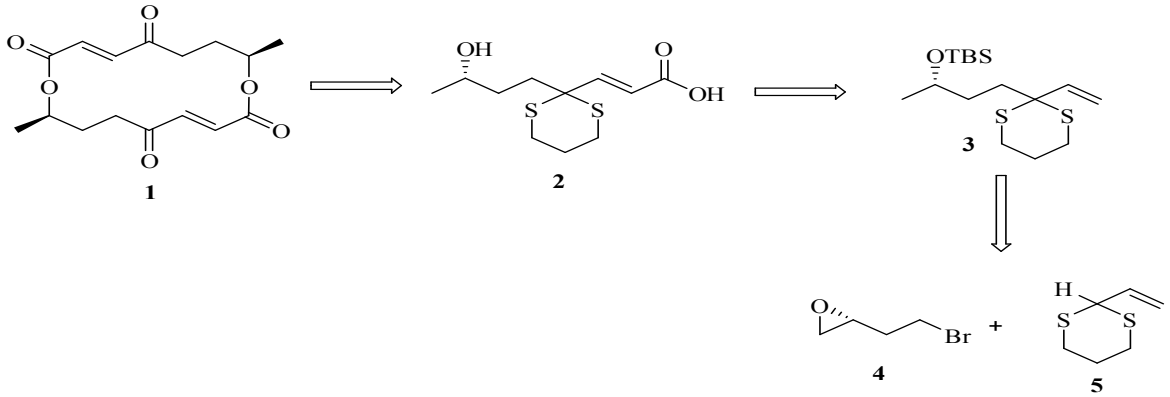
Macrodiolides (macrocyclic dilactones) are well-represented in nature as both homo and heterodimers and offer a wide variety of skeletons, ring sizes, and functional groups. Natural products with macrodiolide frameworks are also known to exhibit a wide range of biological properties including antibiotic, antifungal,[1-3] antihelmintic,[4-6] phytotoxic [7-9] and antileukemic activities.

The macrolide dilactone pyrenophorin is a good antifungal and herbicidal agent and has been isolated from *Pyrenophora avenae*,[10] *Stemphylium radicinum*,[11,3] and *Drechslera avenae*.[8] This C_2-symmetric dilactone is derived by head-to-tail dimerization of two identical C8 units. Due to the promising biological activity and the impressive structural features of (-)-pyrenophorin (**1**), appeared to be an attractive target for total synthesis[12].



(-)-Pyrenophorin (**1**)

Figure 1. (-) Pyrenophorin

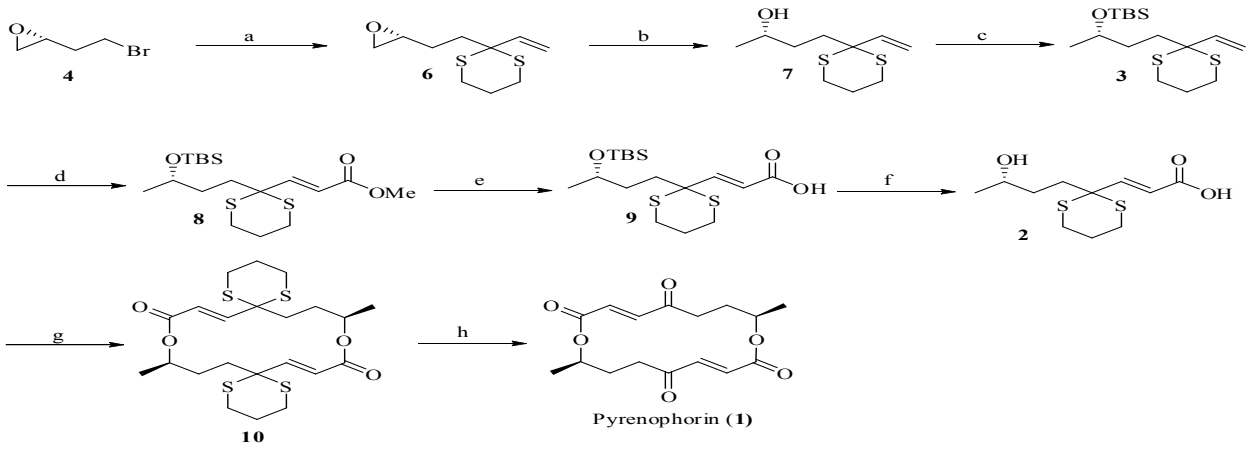


Scheme 1

In continuation of our interest on the total synthesis of biologically active natural products, we herein report the total synthesis of pyrenophorin (**1**) utilizing Regioselective ring opening and the intermolecular Mitsunobu cyclization.

Results and discussion

The retrosynthetic analysis of **1** envisions that it could be obtained from the hydroxy-acid **2** *via* cyclodimerisation under the Mitsunobu reaction conditions followed by deprotection of cyclic thiols. Hydroxy-acid **2** 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 known 2-bromo epoxide **4**[13](Scheme 2) on alkylation with 2-vinyl-1,3-dithiane **5** in dry THF gave compound **6** in 73% yield. Regioselective ring opening of epoxide in compound **6** with LAH in dry THF afforded secondary alcohol **7,** which on subsequent silylation with TBSCl and imidazole in CH_2Cl_2 gave silyl ether **3** in 82% yield. Next, Ozonolysis of **3** in CH_2Cl_2 gave the corresponding aldehyde, which on Wittig reaction with (methoxycarbonylmethylene)triphenyl phosphorane in benzene gave ester **8** in 86% yield.



Scheme 2

***Reagents and conditions*:** (a) **5**,*n*-BuLi, dry THF, -78 ^{o}C, 3 h; b) LAH, dry THF, 0 ^{o}C - rt, 4 h; (c) TBSCl, Imidazole, CH_2Cl_2, rt, 4 h; (d) i) O_3, CH_2Cl_2, -78 ^{o}C, 15 min; ii Ph_3P=CHCOOMe, Benzene, reflux, 2 h. (e) LiOH, THF:MeOH:H_2O (3:1:1), rt, 4 h; (f) TBAF, THF, 0 ^{o}C to rt, 3 h; (g) Ph_3P, DEAD, toluene:THP (10:1) -25 ^{o}C, 10 h; (h) $CaCO_3$, I_2, THF:H_2O (4:1), 0 ^{o}C.

Ester **8** on base hydrolysis (LiOH in THF:MeOH:H_2O-3:1:1) afforded acid **9** which on desilylation with TBAF in dry THF afforded the hydroxy-acid **2** in 86% yield. Hydroxy-acid **2** on cyclodimerisation under the Mitsunobu reaction conditions[14] (Ph_3P and DEAD) at -25 ^{o}C for 10 h furnished **10** in 61% yield. Finally, deprotection of 1,3 dithaine group in compound **10** with $CaCO_3$ and I_2, in THF:H_2O for 5 h afforded the pyrenophorin **1** in 73% yield as a white solid. m.p. 171-173 ^{o}C (lit.[3] m.p. 175 ^{o}C); $[\alpha]_D$ -57.3 (c 0.65, acetone) [lit.[15] $[\alpha]_D$ -54.5 (c 0.48, acetone)]. The ^{1}H and ^{13}C NMR data and optical rotation value of synthetic **1** were in good accordance with data reported in the literature.[16]

Conclusion

In summary, the total synthesis of pyrenophorin **1** was achieved from known 2-bromo epoxide **4**. The key features of this total synthesis include: i) Regioselective ring opening and ii) Mitsunobu cyclodimerisation.

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17. *Spectral data of* 3: $[\alpha]_D$ +82.6 (*c* 0.55, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.87 (m, 1H, olefinic CH), 5.11 (m, 2H, olefinic CH_2), 2.83-2.54 (m, 6H, S$\underline{CH_2}$-$\underline{CH_2}$-S$\underline{CH_2}$), 3.72 (m, 1H, -CH), 1.66-1.40 (m, 4H, 2 x -CH_2), 1.12 (d, 3H, *J* = 6.2 Hz, -CH_3), 0.87 (s, 9H, 3 x -CH_3), 0.08 (s, 6H, 2 x -CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.3, 120.1, 71.3, 56.4, 38.2, 35.3, 27.4, 25.9, 24.1, 23.8, 18.3, -4.3; ESIMS: 355 $(M+Na)^+$, 333 $(M+H)^+$.
18. *Spectral data of* 2: $[\alpha]_D$ -62.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.87 (d, 1H, *J* = 15.8 Hz, olefinic), 6.14 (d, 1H, *J* = 15.8 Hz, olefinic), 3.91 (m, 1H, -OCH), 3.11 (br s, 1H, -OH), 2.88-2.79 (m, 1H, S-CH), 2.73-2.61 (m, 4H, S-CH_2-CH-CH-S), 2.58-2.49 (m, 1H, SCH$_2$-$\underline{CH}$), 1.76-1.63 (m, 2H, -CH_2), 1.55-1.41 (m, 2H, -CH_2), 1.17 (d, 3H, *J* = 6.1 Hz, -CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 174.1, 143.8, 126.3, 70.4, 69.8, 46.3, 35.4, 29.1, 25.0, 23.2; ESIMS: 285 $(M+Na)^+$.

19. *Spectral data of* 1: $[\alpha]_D$ -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 $(M+H)^+$.