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Preparation of Macrodiolides via a Common Chiral Building Block. Total Synthesis of (–)-Pyrenophorin and (–)-Pyrenophorol

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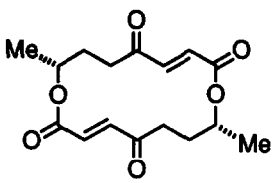
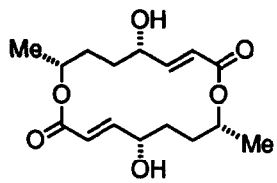
Abstract: Macrodiolides (–)-pyrenophorin and (–)-pyrenophorol have been synthesized utilizing a C_2 symmetric (*R,R*)-diepoxide as a common enantiopure chiral building block.

The macrolide dilactone (diolide) (–)-pyrenophorin (**1**)[1] is an antifungal antibiotic produced by the plant pathogenic fungi *Pyrenophora avenae* and *Stemphylium radicinum*, which is closely related structurally to (–)-pyrenophorol (**2**) isolated from *Byssochlamys nivea*[2a] and *Stemphylium radicinum*.[2b] These naturally occurring diolides are characterized by a 16-membered ring derived by head-to-tail dimerization of two identical C_8 hydroxy acid subunits. Although intensive efforts have been directed toward the synthesis of **1**,[3] almost all synthetic approaches reported are based upon the preparation of the racemic monomeric hydroxy acids followed by dimerization to the diolide, which leads to the formation of 1:1 mixture of the racemic and meso forms of **1**.[3,4] Hitherto, only a few examples of chiral synthesis of the naturally occurring 8*R*,16*R* isomer **1** have been published by Seebach's group[5] and Takano et al.[6] In contrast to the comprehensive work done on **1**, it was only very recently that the first synthesis of pyrenopholrol (**2**) was accomplished,[7] which enabled the relative and absolute natural configurations of **2** to be established.



1 (–)-pyrenophorin

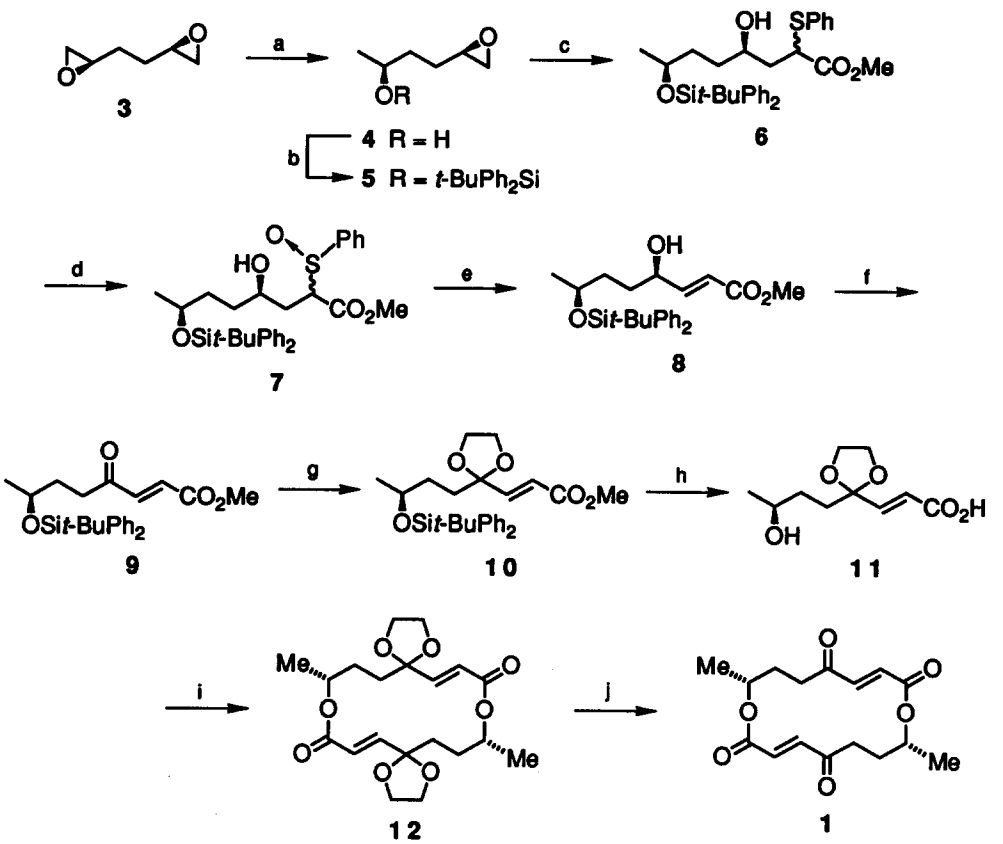


2 (–)-pyrenophorol

Recent investigation from this laboratory has revealed that the chiral C_2 symmetric diepoxide **3** serves as a versatile building block in the preparation of several natural products.[8] In this communication we now report a enantioselective synthesis of these natural diolides **1** and **2** based on a stereo-defined approach utilizing the enantiopure (*R,R*)-diepoxide **3** as a single, common chiral building block.

As shown in Scheme 1, the synthesis of **1** was undertaken to obtain the monoepoxide **4** by monoaddition of hydride ion to the diepoxide **3**[9] which was best effected by using 1 mol equiv of Vitride in THF, leading to the epoxy alcohol **4** in 74% yield based on 40% recovered starting material. After O-silylation (*t*-$BuPh_2SiCl$, DMAP), the resulting monoepoxide **5** was further subjected to ring opening by exposure to (phenylthio)acetic acid dianion ($PhSCH_2CO_2H$, LDA, THF) followed by diazomethane esterification, affording the α-phenylthio-γ-hydroxyester **6** in 48% overall yield from **4**. The sulfoxide **7**, which resulted from sodium metaperiodate

Scheme 1



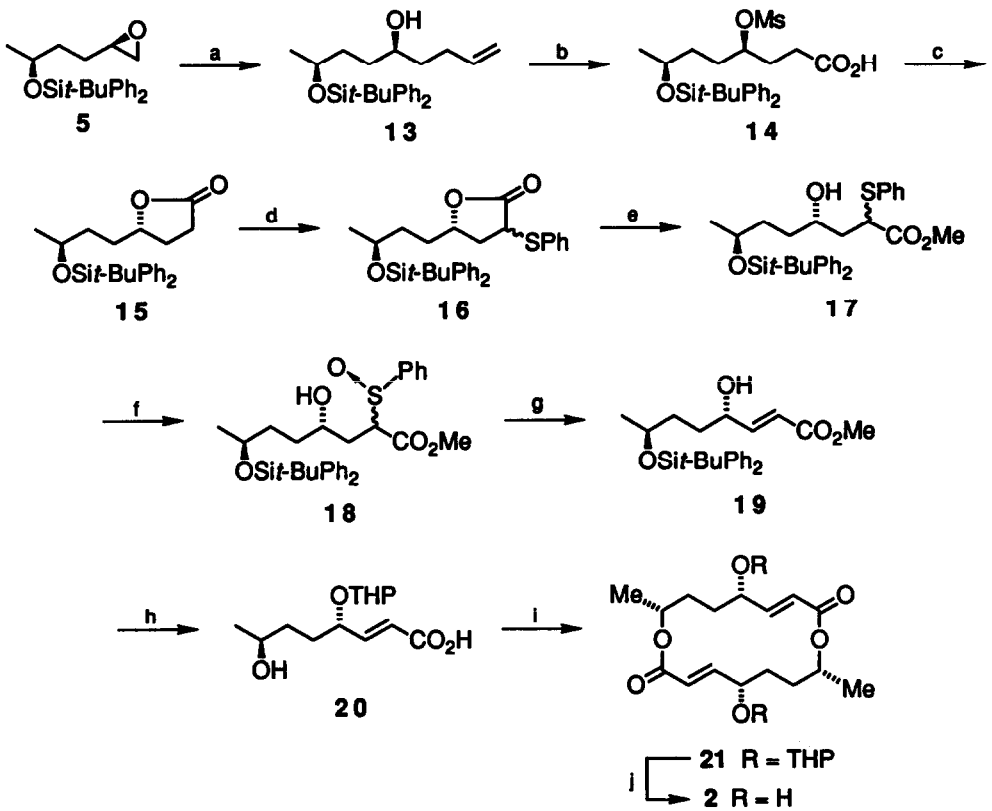
(a) Vitride (1 mol equiv), THF, 0 °C → rt; (b) *t*-$BuPh_2SiCl$, DMAP, CH_2Cl_2, rt; (c) $PhSCH_2CO_2H$, LDA (2 equiv), THF, 0 °C → rt, then CH_2N_2, Et_2O; (d) $NaIO_4$, MeOH–H_2O, rt; (e) Py (2 equiv), toluene, reflux; (f) PDC, DMF, rt; (g) $CH(OEt)_3$, $HO(CH_2)_2OH$, $BF_3{\cdot}OEt_2$, benzene, reflux; (h) 20% NaOH–MeOH, rt, then Bu_4NF, THF, reflux; (i) Ph_3P, DEAD, toluene–THF (10:1), –25 °C, 10 h; (j) CSA, acetone.

oxidation of **6** in aqueous methanol, underwent pyrolysis in boiling toluene in the presence of pyridine to furnish (*E*)-α,β-unsaturated hydroxy ester **8** (85% yield from **6**). Compound **8** was converted to **10** (67% yield) via PDC oxidation and subsequent protection of the resulting ketone as the ethylene ketal. Alkaline hydrolysis of the ester followed by desilylation (Bu_4NF, THF, reflux) provided the hydroxy acid **11** (100%). Cyclodimerization to **12** was carried out under the Mitsunobu conditions according to Gerlach's procedure.[3b] Thus, a reasonably dilute solution of **11** (10^{-2} M) in toluene–THF (10:1) was treated with Ph_3P and DEAD at –25 °C for 10 h to generate the protected pyrenophorin **12** (44% yield). Acidic removal of the carbonyl protecting group furnished (–)-pyrenophorin (**1**) [mp 177–178 °C (lit.[1] mp 175 °C); $[\alpha]^{25}_D$ –55.9° (*c* 0.44, EtOH) [lit.[1] $[\alpha]_D$ –50° (EtOH)[10]], $[\alpha]^{25}_D$ –71.5° (*c* 0.13, acetone) [lit.[5a] $[\alpha]_D$ –54.5° (*c* 0.48, acetone), lit.[6]

$[\alpha]^{26}_D$ –72.9° (*c* 0.650, acetone)] in 80% yield, whose spectra were in accord with those for natural (^{1}H NMR) and synthetic (IR and ^{13}C NMR)[3b,5b] materials of **1**.

We next undertook to elaborate (–)-pyrenophorol (**2**) by utilizing the foregoing monoepoxide **5** as outlined in Scheme 2. Addition of the Grignard reagent (CH_2=$CHCH_2MgCl$) in the presence of CuI to **5** led to ring opening to give the unsaturated alcohol **13** (76%). O-Mesylation and oxidation with RuO_4 gave the carboxylic acid **14** (82%). Treatment of **14** with $KHCO_3$ in aqueous methanol resulted in cyclization to give the γ-lactone **15** (90%) as a single diastereomer: Thus, the stereochemistry at C-4 (in **14**) was inverted in this S_N2 reaction. Introduction of a double bond α,β to the carbonyl group was effectively achieved by application of the sulphenylation–dehydrosulphenylation sequence in a similar manner as described above. Accordingly, the enolate of the γ-lactone **15** generated by using $LiN(SiMe_3)_2$ (HMPA–THF, –78 °C) was treated with

Scheme 2



(a) CH_2=$CHCH_2MgCl$, CuI, THF, –15 °C; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C, then RuO_4, CCl_4–MeCN–H_2O, rt; (c) $KHCO_3$, MeOH–H_2O, rt, 10 min; (d) 1 M $LiN(SiMe_3)_2$ in THF, THF–HMPA, –78 °C, then PhSSPh, THF, –78 °C; (e) 20% aq NaOH, MeOH, rt, then CH_2N_2, Et_2O, 0 °C; (f) mCPBA, –20 °C; (g) Py (2 equiv), toluene, reflux; (h) i, 2,3-dihydropyran, CSA, CH_2Cl_2; ii, 20% aq NaOH, MeOH, rt; iii, Bu_4NF, THF, reflux; (i) Ph_3P, DEAD, toluene–THF (10:1), –25 °C, 10 h; (j) TsOH·H_2O, MeOH, rt.

diphenyl disulfide to afford the α-phenylthio-γ-lactone **16** (72% yield), which was then subjected to hydrolysis followed by diazomethane esterification to give the α-phenylthio-γ-hydroxyester **17** (81% yield). After conversion to the sulfoxide **18** via oxidation with mCPBA, pyrolysis occurred in boiling toluene to generate the (*E*)-α,β-unsaturated hydroxy ester **19** (89% from **17**). After protected as the tetrahydropyranyl ether, the ester was hydrolyzed, and subsequent desilylation afforded the hydroxy carboxylic acid **20**. When **20** was exposed to the Mitsunobu conditions described above for the formation of **12**, the macrolactonization took place with complete inversion of chirality at C-4 to furnish **21** in 59% yield. Removal of the O-protecting group (TsOH, MeOH) provided (–)-pyrenophorol (**2**), mp 138–139 °C (lit.[2a] mp 135 °C); $[\alpha]^{24}_{D}$ –3.6° (*c* 0.36, acetone) [lit.[2a] $[\alpha]^{20}_{D}$ –3° (*c* 1.0, acetone)] in 84% yield. The IR (CH_2Cl_2), ^1H NMR, and CIMS (isobutane) of synthetic **2** were all identical with those of an authentic specimen of (–)-pyrenophorol.

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10. The reported data in ref 1 for optical rotation of **1** omits description of the solvent (EtOH) used; we obtained this infromation directly upon inquiry of Dr. K. Hirai, one of the authors.

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