

## Concise Enantiodivergent Synthesis of Eutypoxide B

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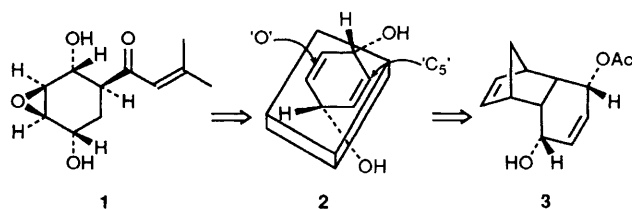
The first enantiodivergent synthesis of eutypoxide B **1**, a metabolite of the fungus *Eutypa lata*, has been accomplished in a stereo- and regio-controlled manner by using the single chiral building block **3** as a chiral equivalent of (Z)-cyclohex-2,5-dien-1,4-diol **2**.

The fungus *Eutypa lata*, the pathogen responsible for vineyard dieback, produces a secondary metabolite eutypoxide B **1** having five stereogenic centres on a cyclohexane ring. The racemic total synthesis of **1** has been reported by Tabacchi and coworkers<sup>2</sup> by employing the Diels–Alder reaction as the key step. However, the key reaction directed the diastereofacial selection in such a way so as to give the diastereoisomeric mixture containing the desired epimer only in a ratio of 1 : 10; fortunately the epimers could be separated in the later stages.<sup>2</sup> We report here the enantiodivergent and stereocontrolled approach to both enantiomers of eutypoxide B **1** starting from the single chiral building block **3** which we have devised.

Because the synthesis of **1** could formally be achieved by regio- and enantio-selective addition of the C<sub>5</sub> subunit and the epoxide oxygen to *meso*-(Z)-1,4-dihydroxycyclohexa-2,5-diene **2** from the *anti*-face to the hydroxy groups, we began the synthesis using the optically pure **3**, obtained by the lipase mediated asymmetrization of a *meso*-precursor,<sup>3</sup> as a chiral equivalent of **2** (Scheme 1). Thus, **3** was first oxidized to the ketone **4**,<sup>†</sup>  $[\alpha]_D^{30} -219.0$  (c 1.29, CHCl<sub>3</sub>),<sup>‡</sup> in 91% yield to carry out regiospecific 1,4-addition. Owing to its biased structure, **4** allowed the 1,4-addition of vinylmagnesium bromide<sup>4</sup> stereospecifically from the less hindered *exo*-face to give the vinyl ketone **5**, m.p. 73–74 °C,  $[\alpha]_D^{32} +20.9$  (c 0.94, CHCl<sub>3</sub>), exclusively, in 81% yield. Reduction of **5** with sodium borohydride again occurred stereospecifically at the *exo*-face

to afford the *endo*-alcohol **6** whose stereochemistry was confirmed by the bromo-ether formation and the reductive reversion by sequential treatment with *N*-bromosuccinimide (NBS) and zinc.<sup>3,5</sup> Practically, **5** was sequentially reduced with sodium borohydride and deacetylated with potassium carbonate in methanol in the same flask to furnish the diol **7**, m.p. 131–132 °C,  $[\alpha]_D^{27} +72.2$  (c 1.16, MeOH), in 92% yield.

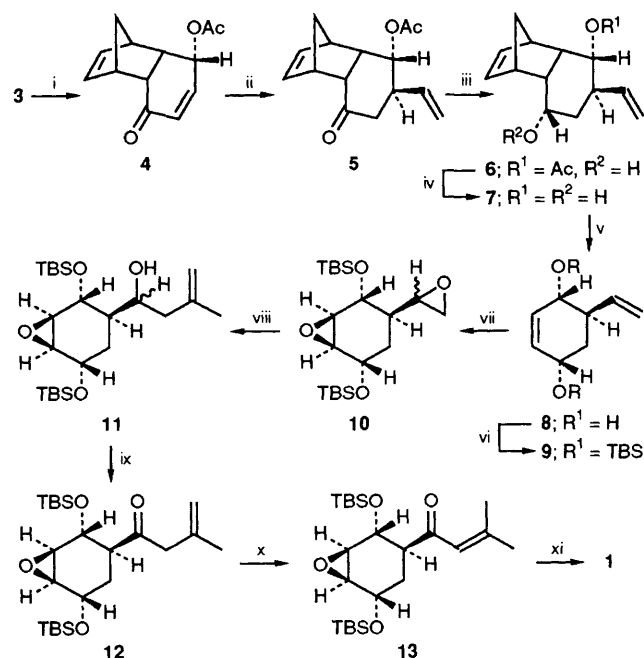
Upon thermolysis in refluxing diphenyl ether<sup>3</sup> (ca. 280 °C, 1 h), **7** gave the substituted cyclohexenediol **8** in 73% yield by retro-Diels–Alder reaction with removal of cyclopentadiene. To install the requisite functional groups in the most efficient way, **8** was first transformed into the disilyl ether **9**,  $[\alpha]_D^{26} -9.4$  (c 1.02, CHCl<sub>3</sub>), in 94% yield, which was then oxidized with an excess amount of *m*-chloroperbenzoic acid (MCPBA) in the presence of radical inhibitor<sup>2,6</sup> to give rise to the diepoxide **10** in 74% yield as a mixture of diastereoisomers being epimeric at the stereogenic centre on the side chain epoxide. The reaction of the mixture with prop-2-enylmagnesium bromide in the presence of copper(I) iodide<sup>7</sup> proceeded chemoselectively at the terminal of the side chain epoxide to give a mixture of the secondary alcohols **11** which, without separation, was oxidized with pyridinium chlorochromate (PCC) to give the single  $\beta,\gamma$ -enone **12**, m.p. 78–79 °C,  $[\alpha]_D^{29}$



Scheme 1

<sup>†</sup> All new isolable compounds showed satisfactory analytical (combustion and/or high resolution mass) and spectral (IR, <sup>1</sup>H NMR and mass) data.

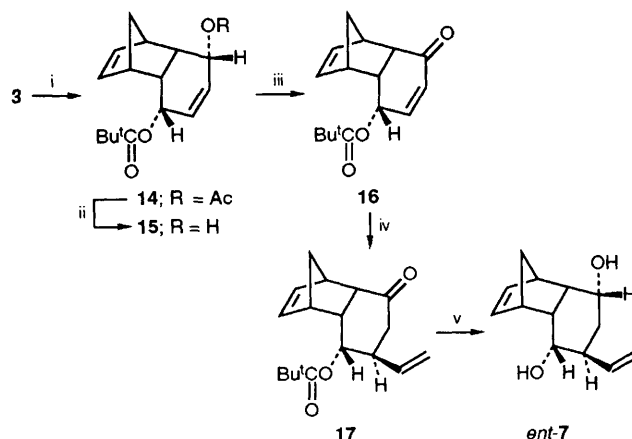
<sup>‡</sup> Optical purity was determined to be >99.5% enantiomeric excess by HPLC (Chiralcel OD, 2% Pr<sup>i</sup>OH–hexane).



**Scheme 2** Reagents and conditions: i, PCC,  $\text{CH}_2\text{Cl}_2$ , room temp.; ii, vinylmagnesium bromide, trimethylsilyl chloride (TMSCl),  $\text{CuBr}\cdot\text{Me}_2\text{S}$ , tetrahydrofuran (THF)–hexamethylphosphoramide (HMPA),  $-78^\circ\text{C}$ , then 5% HCl; iii,  $\text{NaBH}_4$ , MeOH,  $0^\circ\text{C}$ ; iv,  $\text{K}_2\text{CO}_3$ , room temp.; v, diphenyl ether, reflux, 45 min; vi, *tert*-butyldimethylsilyl chloride (TBSCl), imidazole, dimethylformamide (DMF), room temp.; vii, MCPBA (3 equiv.), 4,4'-thiobis(6-*tert*-butyl-*m*-cresol) (10 mol %),  $(\text{CH}_2\text{Cl}_2)_2$ , reflux, 1 h; viii, prop-2-enylmagnesium bromide, CuI, THF,  $-25^\circ\text{C}$ ; ix, PCC,  $\text{CH}_2\text{Cl}_2$ , room temp.; x, DBU (1 equiv.),  $\text{CH}_2\text{Cl}_2$ , room temp.; xi,  $\text{Bu}_4\text{NF}$ , THF, room temp.

+18.3 ( $c$  0.71,  $\text{CHCl}_3$ ), in 89% overall yield. On exposure to 1,8-diazabicyclo[5.4.0]undecene (DBU) in dichloromethane, **12** afforded the  $\alpha,\beta$ -enone **13**,  $[\alpha]_{\text{D}}^{28} +8.0$  ( $c$  0.46,  $\text{CHCl}_3$ ), in 91% yield by facile isomerization. Finally, desilylation of **13** gave (–)-eutypoxide **B 1**,  $[\alpha]_{\text{D}}^{23} -56.6$  ( $c$  0.68,  $\text{CHCl}_3$ ), in 63% yield, whose spectral data were identical with those reported<sup>2</sup> (Scheme 2).

In order to obtain enantiomeric (+)-eutypoxide **B** (*ent*-**1**), **3** was first transformed into the mixed diester<sup>3</sup> **14** which was then treated with methanolic potassium carbonate to give the monoester **15** in 85% overall yield. Oxidation of **15** with PCC, followed by treating the resulting enone **16**,  $[\alpha]_{\text{D}}^{30} +233.0$  ( $c$  1.08,  $\text{CHCl}_3$ ),<sup>‡</sup> obtained in 94% yield, with vinylmagnesium bromide in the presence of copper(I) bromide and trimethylsilyl chloride<sup>4</sup> allowed stereoselective 1,4-addition to



**Scheme 3** Reagents and conditions: i,  $(\text{Bu}^t\text{CO})_2\text{O}$ , 4-*N,N*-dimethylaminopyridine,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , room temp.; ii,  $\text{K}_2\text{CO}_3$ , MeOH, room temp.; iii, PCC,  $\text{CH}_2\text{Cl}_2$ , room temp.; iv, vinylmagnesium bromide, TMSCl,  $\text{CuBr}\cdot\text{Me}_2\text{S}$ , THF–HMPA,  $-78^\circ\text{C}$ , then 5% HCl; v,  $\text{LiAlH}_4$ , THF,  $0^\circ\text{C}$

give the single ketone **17**. On sequential reduction with sodium borohydride and lithium aluminium hydride **17** gave the *ent*-**7**, m.p.  $132\text{--}133^\circ\text{C}$ ,  $[\alpha]_{\text{D}}^{30} -72.5$  ( $c$  0.48, MeOH), in satisfactory overall yield. This constitutes the synthesis of *ent*-(+)-eutypoxide **B** (*ent*-**1**) in the formal sense.

In summary, the present enantiodivergent approach is compatible with the synthesis of both enantiomers of eutypoxide **B 1** though the absolute structure of the natural product has yet to be reported.

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