Concise Enantiodivergent Synthesis of Eutypoxide B

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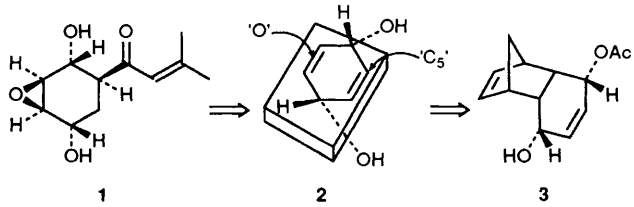
The first enantiodivergent synthesis of eutypoxide B **1**, a metabolite of the fungus *Eutypa lata*, has been accomplished in a stereo- and regio-controlled manner by using the single chiral building block **3** as a chiral equivalent of (*Z*)-cyclohex-2,5-dien-1,4-diol **2**.

The fungus *Eutypa lata*, the pathogen responsible for vineyard dieback, produces a secondary metabolite eutypoxide B[1,2] **1** having five stereogenic centres on a cyclohexane ring. The racemic total synthesis of **1** has been reported by Tabacchi and coworkers[2] 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.[2] We report here the enantiodivergent and stereocontrolled approach to both enantiomers of eutypoxide B **1** starting from the single chiral building block[3] **3** which we have devised.

Because the synthesis of **1** could formally be achieved by regio- and enantio-selective addition of the C_5 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,[3] as a chiral equivalent of **2** (Scheme 1). Thus, **3** was first oxidized to the ketone **4**,† $[\alpha]_D^{30}$ −219.0 (*c* 1.29, $CHCl_3$),‡ in 91% yield to carry out regiospecific 1,4-addition. Owing to its biased structure, **4** allowed the 1,4-addition of vinylmagnesium bromide[4] 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, $CHCl_3$), 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.[3,5] Practically, **5** was sequentially reduced with sodium borohydride and deacylated 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[3] (*ca.* 280 °C, 1 h), **7** gave the subsituted 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, $CHCl_3$), in 94% yield, which was then oxidized with an excess amount of *m*-chloroperbenzoic acid (MCPBA) in the presence of radical inhibitor[2,6] 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[7] 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 β,γ-enone **12**, m.p. 78–79 °C, $[\alpha]_D^{29}$

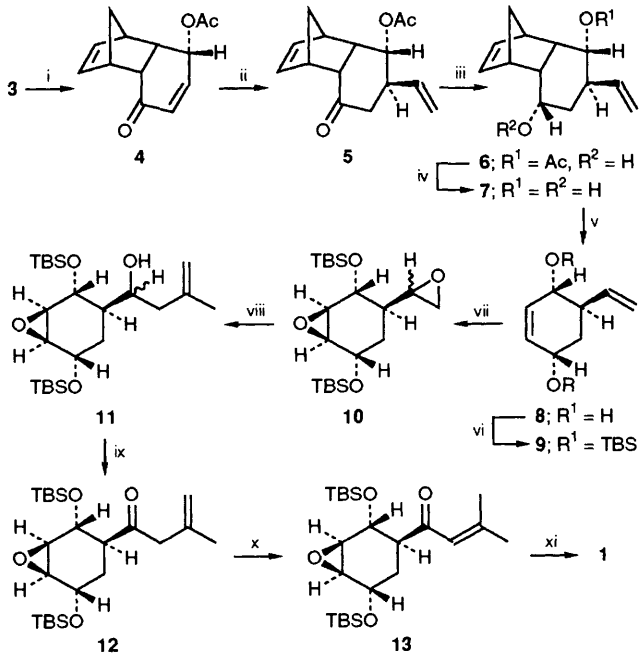


1 2 3

Scheme 1

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

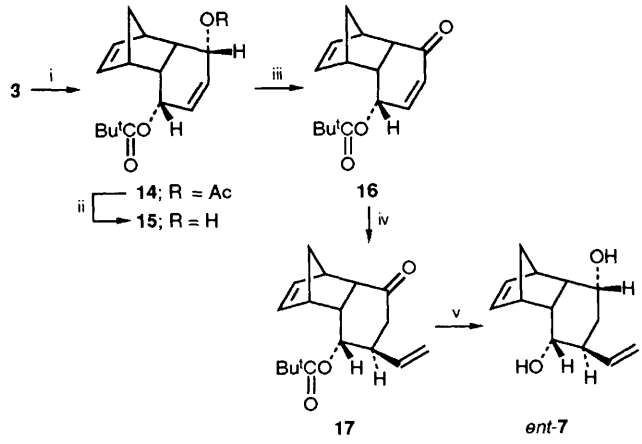
‡ Optical purity was determined to be >99.5% enantiomeric excess by HPLC (Chiralcel OD, 2% Pr^iOH–hexane.



Scheme 2 *Reagents and conditions*: i, PCC, CH_2Cl_2, room temp.; ii, vinylmagnesium bromide, trimethylsilyl chloride (TMSCl), CuBr·Me_2S, tetrahydrofuran (THF)–hexamethylphosphoramide (HMPA), −78 °C, then 5% HCl; iii, $NaBH_4$, MeOH, 0 °C; iv, K_2CO_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%), $(CH_2Cl)_2$, reflux, 1 h; viii, prop-2-enylmagnesium bromide, CuI, THF, −25 °C; ix, PCC, CH_2Cl_2, room temp.; x, DBU (1 equiv.), CH_2Cl_2, room temp.; xi, Bu_4NF, THF, room temp

+18.3 (*c* 0.71, $CHCl_3$), in 89% overall yield. On exposure to 1,8-diazabicyclo[5.4.0]undecene (DBU) in dichloromethane, **12** afforded the α,β-enone **13**, $[\alpha]_D^{28}$ +8.0 (*c* 0.46, $CHCl_3$), in 91% yield by facile isomerization. Finally, desilylation of **13** gave (−)-eutypoxide B **1**, $[\alpha]_D^{23}$ −56.6 (*c* 0.68, $CHCl_3$), in 63% yield, whose spectral data were identical with those reported[2] (Scheme 2).

In order to obtain enantiomeric (+)-eutypoxide B (*ent*-**1**), **3** was first transformed into the mixed diester[3] **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**, $[\alpha]_D^{30}$ +233.0 (*c* 1.08, $CHCl_3$),‡ obtained in 94% yield, with vinylmagnesium bromide in the presence of copper(I) bromide and trimethylsilyl chloride[4] allowed stereoselective 1,4-addition to



Scheme 3 *Reagents and conditions*: i, $(Bu^tCO)_2O$, 4-*N*,*N*-dimethylaminopyridine, Et_3N, CH_2Cl_2, room temp.; ii, K_2CO_3, MeOH, room temp.; iii, PCC, CH_2Cl_2, room temp.; iv, vinylmagnesium bromide, TMSCl, CuBr·Me_2S, THF–HMPA, −78 °C, then 5% HCl; v, $LiAlH_4$, THF, 0 °C

give the single ketone **17**. On sequential reduction with sodium borohydride and lithium aluminium hydride **17** gave the *ent*-**7**, m.p. 132–133 °C, $[\alpha]_D^{30}$ −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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