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Chemoenzymatic Synthesis of (–)-Ribisins A and B from Dibenzo[*b,d*]furan

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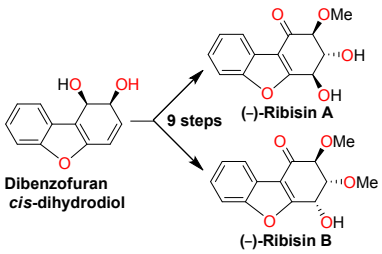
ABSTRACT: *cis*-Dihydrodiols, derived from monocyclic aromatic compounds, are valuable chiral pool intermediates for the synthesis of cyclic natural products. A drawback of this approach, to the synthesis of polycyclic secondary metabolites, is that additional rings must be annulated. To date, relatively few chiral natural products have been synthesized from polycyclic arene *cis*-dihydrodiols. Fungal metabolites, (–)-ribisins A and B, have now been obtained by functional group manipulation of a tricyclic arene metabolite, obtained from toluene dioxygenase-catalyzed regioselective and stereoselective *cis*-dihydroxylation of dibenzo[*b,d*]furan. The synthetic sequences were marginally shorter than the alternative routes, using monocyclic arene *cis*-dihydrodiols and required no carbon-carbon bond-forming reactions.



INTRODUCTION

The dibenzo[*b,d*]furan (dibenzofuran) skeleton is present in a number of biologically interesting chiral natural products, including (+)-galanthamine, opiates *e.g.* (–)-morphine, and the (–)-ribisins (Figure 1). Ribisins are a family of polyoxygenated dibenzofuran derivatives, which were isolated by Fukuyama and co-workers, from the fruiting bodies of the white rot fungus *Phellinus ribis*.[1] This microbial species has a history of use in traditional medicines where it was used to enhance immunity, as well as to treat gastrointestinal cancer, liver disease, cardiovascular disease and diabetes.[2-4] Ribisins A-D, in particular, enhance the ability of nerve growth factor to promote neurite outgrowth in PC12 cells and may have potential in the treatment of stroke, brain trauma and Alzheimer's disease.[1]

Two approaches to the synthesis of ribisins have, to date, been reported.[5-7] The key step in Du's synthetic approach was to use a Ferrier rearrangement of an enol ether, derived from α-D-glucopyranose, generating all three stereocentres of (–)-ribisin A with the correct absolute configurations.[5] Banwell's seminal syntheses were chemoenzymatic and used a chiral *cis*-dihydrodiol, derived from bromobenzene, as starting material.[6, 7] This approach not only gave additional material for further biological evaluation but also led to a correction of the published absolute configuration for (–)-ribisin C and the relative stereochemistry for (–)-ribisin B, where two out of the three stereocentres were reassigned.

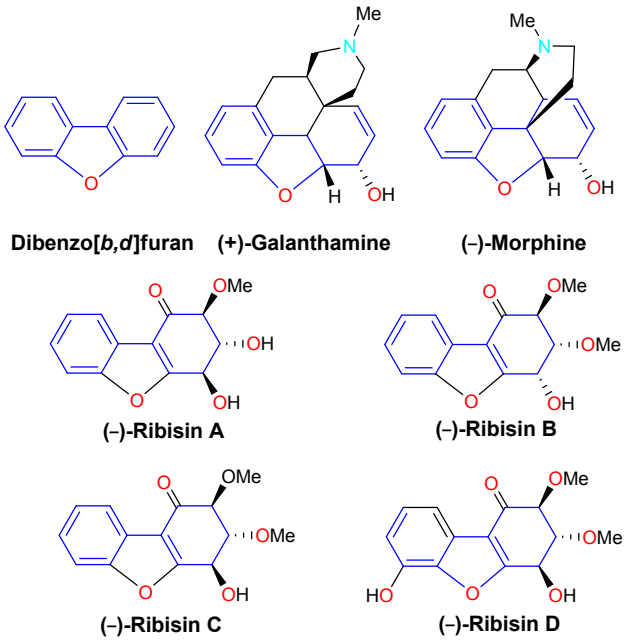
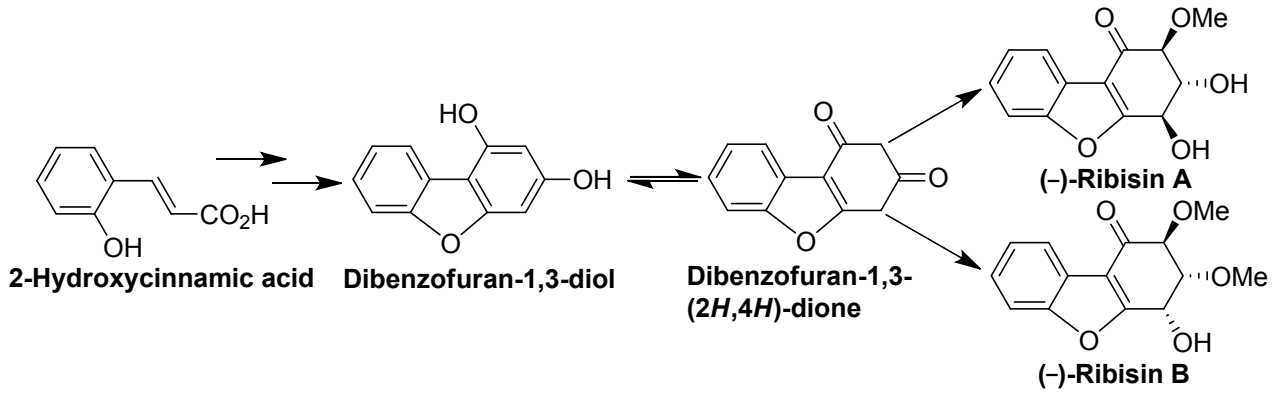


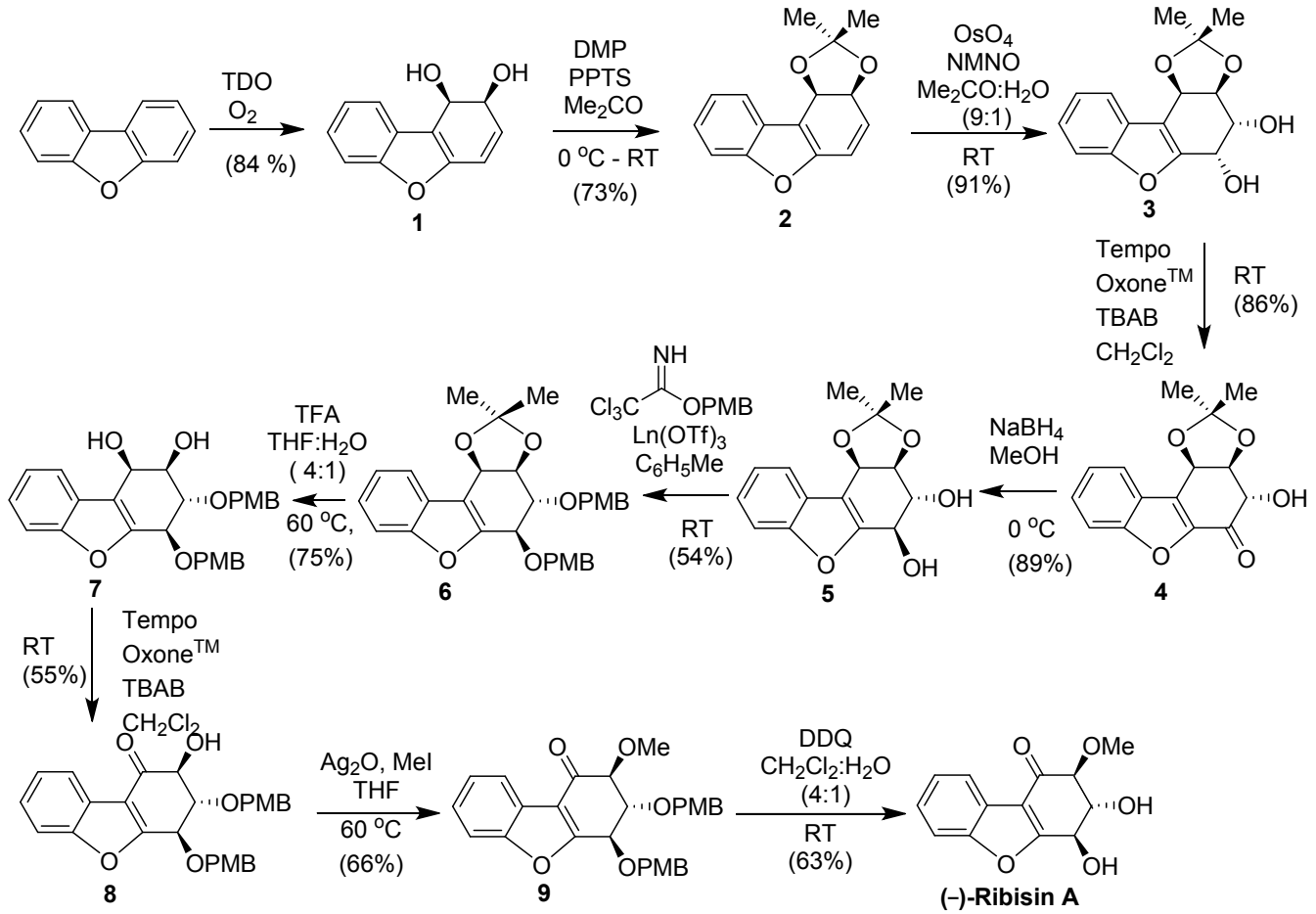
Figure 1. Examples of natural products containing dibenzo[*b,d*]furan subunits .

The structures of (–)-ribisins B and C shown in Figure 1 are thus the corrected versions determined by Banwell *et al*. [6, 7] A possible biosynthetic pathway, to (–)-ribisins A-D from 2-hydroxycinnamic acid in *P. ribis*, *via* oxidoreductase-catalyzed reactions, was reported by Fukuyama *et al.*[1]

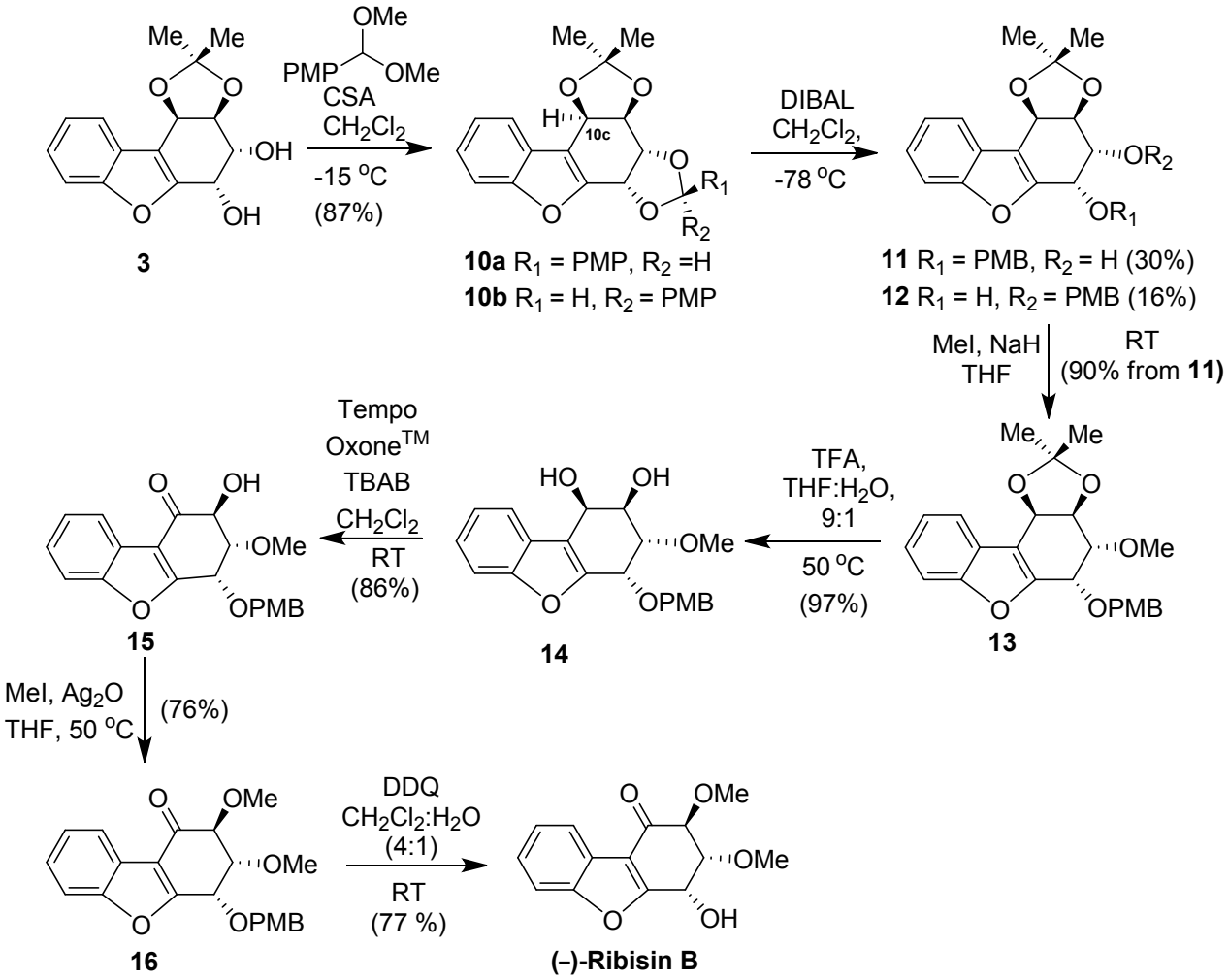
This proposed route involved the formation of an intermediate dibenzofuran-1,3-(2*H*,4*H*)-dione tautomer of dibenzofuran-1,3-diol, and enzyme-catalyzed oxidations to yield (–)-ribisins A and B. Monooxygenase-catalyzed epoxidation of benzoate esters to form arene oxides, oxepines and phenols,[8] and laccase- catalyzed oxidation of phenols were reported using *P. ribis* cultures.[9] The postulated biosynthetic sequence, through a substituted dibenzofuran precursor prompted the current chemoenzymatic approach to (–)-ribisins A and B from dibenzofuran (Scheme 1).



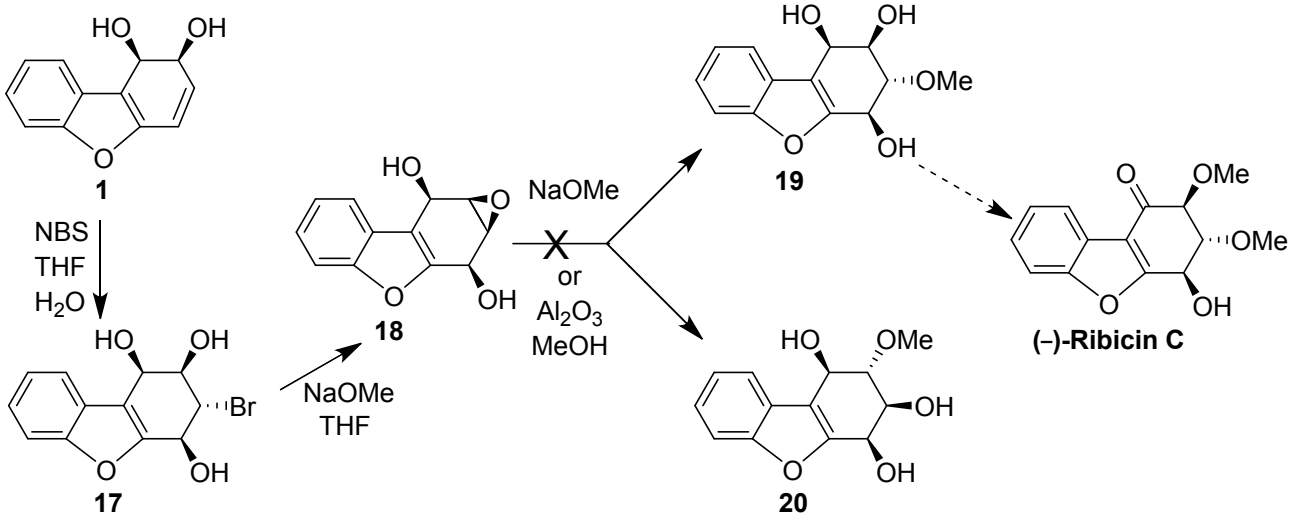
Scheme 1. Proposed biosynthetic route to (–)-ribisins A and B from 2-hydroxycinnamic acid and a dibenzofuran-1,3-diol intermediate



Scheme 2. Synthesis of (–)-ribisin A



Scheme 3. Synthesis of (–)-ribisin B



Scheme 4. Attempted synthesis of (–)-ribisin C

Biotransformations of monocyclic aromatic compounds are routinely utilized, to produce enantiopure *cis*-dihydrodiol metabolites for application in the chemoenzymatic synthesis of natural products.[6, 7, 10-19] Conversely, *cis*-dihydrodiol metabolites, from polycyclic arenes or heteroarenes, are rarely used in chemoenzymatic synthesis.[20] Thus, although the isolation and stereochemical assignment of *cis*-dihydrodiols from tricyclic aromatic substrates was reported, using naphthalene dioxygenase (NDO)[21] or biphenyl dioxygenase (BPDO)[20-23] as biocatalysts, few examples of their employment as homochiral synthons have been documented. Furthermore, biotransformations of polycyclic arene substrates, with the latter dioxygenase types, often resulted in the formation of mixtures of *cis*-dihydrodiol isomers in relatively low yields. Biotransformations, using the UV4 mutant strain of the soil bacterium *P. putida* and *E. coli* recombinant strains, both expressing toluene dioxygenase (TDO), have been widely used in arene *cis*-dihydroxylations. In our laboratories, anilines, phenols, phenolic ethers, dibenzothiophene and dibenzofuran are among the more unexpected substrates recently found to undergo TDO-catalyzed *cis*-dihydroxylations.[24-27]

One possible chemoenzymatic approach to the synthesis of (–)-ribisins, was to start with dibenzofuran as substrate, and then to add the two oxygen atoms to the *cis*-dihydrodiol metabolite in a stereo-controlled manner. This approach had the advantage that no carbon-carbon bond-forming reactions occurred in the entire synthetic sequence and the number of steps in the synthesis could, in principle, be reduced.

RESULTS AND DISCUSSION

Based on predictions, from molecular docking studies, and the use of *P. putida* UV4 whole cells (as TDO source), biotransformation of dibenzofuran resulted in exclusive *cis*-dihydroxylation at the pseudo-bay region leading to the isolation of metabolite **1** (84% yield), with no evidence of other *cis*-dihydrodiol isomers being formed.[27] *cis*-Diol **1**, with dearomatization in one of the rings, was ideally functionalized for conversion to (–)-ribisins A and B as it was enantiopure (>98% *ee*) and had the required (1*S*,2*S*) absolute configuration, based on X-ray crystallographic analysis of a *cis*-diol epoxide derivative (Scheme 2-4).[27]

Starting from dibenzofuran *cis*-dihydrodiol **1**, a nine-step synthesis of (–)-ribisin A is outlined (Scheme 2). *cis*-Diol **1** was found to be acid-sensitive and readily dehydrated regioselectively, to give dibenzofuran-2-ol. Using the weak acid catalyst PPTS, *cis*-diol **1** was converted to acetonide **2** in 73 % yield along with the dehydration product dibenzofuran-2-ol (11 % yield). During the TDO-catalyzed biotransformation of dibenzofuran, traces of a further *cis*-dihydrodiol metabolite, derived from *cis*-dihydroxylation of dibenzofuran-2-ol, was also detected.[27]

cis-Dihydroxylation of alkene **2**, employing Upjohn osmylation conditions,[28] proceeded as expected, exclusively, from the face *anti* to the bulky acetonide protecting group, to give the *cis*-diol acetonide diastereoisomer **3** (91% yield). Due to the steric bulk of the acetonide group, attempted Mitsunobu inversion of configuration, at the C-4 chiral alcohol center of compound **3** was unsuccessful in our hands. The stereoinversion was later achieved in two steps, by a chemoselective oxidation of the more activated alcohol group of diol **3** to form α-hydroxyketone **4**, followed by a stereoselective reduction to give *trans*-diol **5**. Although a number of methods was available, for the chemoselective oxidation of activated alcohols, a problem arose in this particular case; the oxidation product, α-hydroxyketone **4**, was found to be very sensitive to further oxidation, leading to carbon-carbon bond cleavage. After screening oxidation protocols, it was found that chemoselective oxidation with Oxone™ in the presence of TEMPO,[29] yielded α-hydroxyketone **4** in 86% yield. Sodium borohydride reduction of ketone **4** gave exclusively *trans*-diol **5** in 89% yield, which was protected as *bis*-*p*-methoxybenzyl ether **6** (54% yield). The acetonide group of ketal **6** was removed under acidic conditions, to furnish the resulting *cis*-diol **7** (75% yield). Chemoselective oxidation (TEMPO, Oxone™) of the C-1 hydroxyl group located within the hindered pseudo-bay region of *cis*-diol **7** gave α-hydroxyketone **8** (55% yield). The alcohol group of ketone **8** was converted (Ag_2O/MeI) to methyl ether **9** (66% yield). In the final step, oxidative removal of the PMB protecting groups using DDQ gave (–)-ribisin A in 63% yield. The spectroscopic properties of the synthetic sample were in good agreement with the natural product obtained from *P. ribis*. The synthesis of (–)-ribisin A, from dibenzofuran *cis*-dihydrodiol **1**, was accomplished in nine steps (9% overall yield), a modest improvement over fourteen and eleven steps from the previous two routes.[5-7]

cis-Diol **3** also proved to be a versatile intermediate for the synthesis of (–)-ribisin B (Scheme 3) as all stereocentres already had the correct absolute configurations. To complete its synthesis, regisoselective *O*-methylation and alcohol oxidation to form a ketone were required. Reaction of diol **3** with anisaldehyde dimethyl acetal formed an *exo*:*endo* mixture (57:43) of anisylidene acetal diastereoisomers **10a**:**10b**. Due to the strong relaxation of the acetal protons (R_2 or R_1 =H) by the *ortho* proton on the PMP group, distant nOe values were not observed and, therefore, the *exo* isomer **10a** and *endo* isomer **10b** could not be assigned by this method. However, the chemical shift for C-10c proton in diol **3** was 5.42 ppm while in acetals **10a** and **10b** the chemical shifts of the corresponding pseudo-bay region protons were 5.44 and 5.62 ppm respectively. This indicates that the *p*-methoxyphenyl group of the minor *endo* acetal isomer **10b** is pseudo-axial and proximate to the C-10c proton. This premise was tentatively used to differentiate between the *exo* and *endo* isomers. The difference in chemical shift (0.32 ppm) of the acetal protons **10a** (R_2 6.02 ppm) and **10b** (R_1 5.70 ppm) can be rationalised by the proximity of proton R_2 to the benzofuran ring, lending further tentative support to the stereochemical assignment. Attempts to regioselectively alkylate diol **3** using sodium hydride and PMB-Cl were unsuccessful.

After careful multiple elution PLC, only the minor *endo* diastereoisomer **10b** could be fully separated from a small sample of the mixture. DIBAL reduction of acetal **10b** gave, exclusively the unwanted PMB-ether **12**. Reduction (DIBAL) of the original mixture of acetal diastereoisomers **10a**/**10b** (57:43) yielded a further mixture (58:42) of readily separable alcohols **11** (30% yield) and **12** (16% yield). The selectivity for the desired *exo*-acetal **10a** may be improved by synthesis of the more sterically demanding 2,4-dimethoxyphenyl acetal. Methylation (MeI/NaH) of alcohol **11** yielded methyl ether **13** (90% yield). The ketal group in methyl ether **13** was cleaved, under acidic conditions (TFA, THF, H_2O), in a similar manner to that used for acetonide **6** (Scheme 2), to form *cis*-diol **14** (97% yield). The unwanted regioisomer **12** could, in principle also be converted to intermediate **13** through protecting group manipulation, but this route was not investigated. The C-1 hydroxyl group of diol **14** was chemoselectively oxidized to ketone **15** (catalytic TEMPO with Oxone™, Scheme 3) (86% yield). Methylation (Ag_2O/MeI) of α-hydroxy ketone **15** gave dimethoxy ketone **16** (76% yield). Finally, the PMB protecting group was oxidatively removed (DDQ, H_2O, CH_2Cl_2), from PMB-ether **16**, to furnish (–)-ribisin B (77% yield) in10% overall yield from *cis*-dihydrodiol **1** over nine steps.

As part of an earlier study of biotransformations (P. putida UV4) of tricylic heteroarenes, the isolation of (1*S*,2*S*)-dihydrodiol metabolite **1**, and its potential as a chiral synthon, was demonstrated by the synthesis and absolute configuration assignment of the diol epoxide derivative **18** by X-ray crystallography, via treatment of bromohydrin intermediate **17** with sodium methoxide.[27] The possibility of epoxide **18** undergoing nucleophilic attack by methoxide anion, using different solvents and temperatures, to yield triols **19** and **20**, was examined (Scheme 4). Despite these changes in reaction conditions neither of the triols was obtained. Reactions of unactivated diol epoxides toward nucleophilic attack had been reported by using Al_2O_3 in MeOH solution.[30] However, under similar reaction conditions, the required triol **19** was not observed among the range of unidentified products. An alternative synthetic approach to (–)-ribisin C, using chiral intermediate **4**, is currently under investigation.

CONCLUSION

The chemoenzymatic syntheses of natural products, from *cis*-dihydrodiol metabolites, have generally been restricted to those obtained from monocyclic arene substrates.[6-8, 10-19] *cis*-Dihydrodiols of acridine and dictamnine, obtained by BPDO-catalyzed *cis*-dihydroxylation, were among the few examples of tricyclic arenes utilized in the chemoenzymatic synthesis of secondary metabolites.[20] Following on from the innovative use of a monocyclic arene *cis*-dihydrodiol of bromobenzene in chemoenzymatic syntheses,[6, 7] this study has demonstrated that a tricyclic *cis*-dihydrodiol, formed by TDO-catalyzed *cis*-dihydroxylation of dibenzofuran,[27] can also be used as a precursor for the asymmetric synthesis of (–)-ribisins A and B. This alternative approach of using a polycyclic *cis*-dihydrodiol precursor can now be added to the available methods for the synthesis of chiral natural products containing benzofuran rings.[31]

EXPERIMENTAL SECTION

^{1}H and ^{13}C{1H} NMR spectra were recorded on Bruker AV-400 and AV-600 instruments using specified solvents. Chemical shifts (δ) are reported in ppm relative to $SiMe_4$ and coupling constants (J) are given in Hertz (Hz). Optical rotations ($[\alpha]_D$) measurements (10^{-1} deg cm^2 g^{-1}) were carried out at ambient temperatures (20-25^o C) on a Perkin-Elmer 214 polarimeter and specified solvent concentration (g /100 mL) at the sodium D-line (589 nm). IR spectra were recorded in KBr disc or in thin film. Mass spectra (ES) were recorded on an LCT Premier Mass Spectrometer using an ESI-TOF analyser. Accurate molecular weights were obtained by the peak matching method, using heptacosafluorotributylamine as the standard reference, and were accurate to within ±5 x 10^{-6} ppm. Melting points were recorded in degrees Celsius using a Stuart SMP10 melting point apparatus. Merck Kieselgel $60F_{254}$ analytical plates were used for TLC analyses. Thermostatically controlled oil baths were used for reactions at elevated temperatures. Preparative layer chromatography (PLC) separations were carried out on glass plates (20 cm x 20 cm) coated with Merck Keiselgel $PF_{254/366}$ silica gel (21 g silica gel in 62 mL water). Flash column chromatography was performed on Fluorochem silicagel 60A 40-63u.

*(1R,2S)-1,2-Dihydrodibenzo[b,d]furan-1,2-diol (**1**).*

Dibenzofuran was biotransformed using (*P. putida* UV4) according to the literature procedure, to give diol **1** in excellent yield (84%).[27] This product was used in the current study.

*(3aR,10cS)-2,2-Dimethyl-3a,10c-dihydrobenzo[b][1,3]dioxolo[4,5-e]benzofuran (**2**).*[22] To a stirred solution of *cis*-dihydrodiol **1** (270 mg, 1.34 mmol) in a mixture of acetone (6 mL) and 2,2-DMP (6 mL), maintained at 0°C, was added pyridinium *p*-toluenesulfonate (PPTS, 234 mg, 0.93 mmol). The reaction mixture was stirred (2 h) at 0°C and then at room temperature for 12 h. After the addition of a saturated aqueous solution of $NaHCO_3$ (5 mL), the mixture was concentrated under reduced pressure and extracted with EtOAc (2 x 15 mL). The organic phase was dried (Na_2SO_4), concentrated and the crude product purified by flash column chromatography (4% EtOAc in hexane), to afford acetonide **2**, a white solid, (237 mg, 73%); R_f = 0.4 (10% EtOAc in hexane); $[\alpha]_D^{22}$ +130.8 (*c* 0.66, $CHCl_3$); HRMS (ES) calc. for $C_{15}H_{14}O_3Na$ $(M + Na)^+$ 265.0836 found 265.0841; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.65 (m, 1H), 7.45 (m, 1H), 7.26 (m, 2H), 6.57 (dd, J = 10.0, 1.3 Hz, 1H), 6.08 (dd, J = 10.0, 3.5 Hz, 1H), 5.43 (d, J = 8.3 Hz, 1H), 5.00 (ddd, J = 8.3, 3.5, 1.3 Hz, 1H), 1.52 (s, 3H), 1.38 (s, 3H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 155.1, 151.3, 129.2, 127.1, 124.5, 123.5, 119.5, 118.0, 111.6, 111.0, 106.6, 73.0, 69.6, 27.0, 25.1; IR ν_{max}/cm^{-1} 2068, 1935, 1446. ^{1}H NMR data was in good agreement with literature values.

The side product, dibenzo[*b,d*]furan-2-ol (27 mg, 11%), was also isolated from the crude product. NMR data in good agreement with literature values.[32] ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.86 (d, J = 7.8 Hz, 1H), 7.53 (d, J = 8.2 Hz, 1H), 7.44 (td, J = 7.1, 1.3 Hz, 1H), 7.42 (d, J = 8.8 Hz, 1H), 7.36 (d, J = 2.7 Hz, 1H), 7.30 (1H, td, J = 7.5, 0.9 Hz, H), 6.95 (1H, dd, J = 8.8, 2.7 Hz, 1H), 4.98 (1H, br s, OH); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ_C 157.0, 151.5, 151.0, 127.3, 125.1, 124.2, 122.5, 120.7, 115.3, 112.1, 111.8, 106.3.

*(3aS,4R,5S,10cR)-2,2-Dimethyl-3a,4,5,10c-tetrahydrobenzo[b][1,3]dioxolo[4,5-e]benzofuran-4,5-diol (**3**)*. To a stirred solution of acetonide **2** (17.5 mg, 0.072 mmol) and *N*-methylmorpholine-*N*-oxide (10.0 mg), in a mixture of acetone (4.5 mL) and water (0.5 mL), maintained at 0°C, was added a solution of osmium tetroxide in ^{t}BuOH (2.5 wt %, 70 µl). After stirring the reaction mixture overnight at room temperature, a saturated aqueous solution of $Na_2S_2O_5$ (1 mL) was added to it and the stirring continued for another 10 mins. The reaction mixture was concentrated under reduced pressure, water (2 mL) added to it, the mixture thoroughly extracted with EtOAc (2 x 5 mL) and the organic extract was dried (Na_2SO_4) and concentrated. The crude product obtained was purified by flash column chromatography (60% EtOAc in hexane) to afford *cis*-diol **3** (18.2 mg, 91%), a white solid, R_f = 0.2 (40% EtOAc in hexane): $[\alpha]_D^{22}$ +30.6 (*c* 0.36, MeOH); HRMS (ES) calc. for $C_{15}H_{16}O_5Na$ $(M + Na)^+$ 299.0887 found 299.0895; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 7.67 (m, 1H), 7.50 (m, 1H), 7.33 (dt, *J* = 7.3, 1.3 Hz, 1H), 7.28 (dt, *J* = 7.5, 1.3 Hz, 1H), 5.42 (d, *J* = 5.5 Hz, 1H), 5.02 (d, *J* = 3.9 Hz, 1H), 4.60 (dd, *J* = 7.3, 5.5 Hz, 1H), 4.26 (dd, *J* = 7.3, 3.9 Hz, 1H), 2.88 (br s, 1H), 2.76 (br s, 1H), 1.52 (s, 3H,), 1.41 (s, 3H,). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ_C 155.9, 151.9, 126.4, 125.3, 123.4, 120.2, 113.0, 111.8, 111.0, 71.8, 69.5, 64.0, 29.7, 28.21, 26.3; IR ν_{max}/cm^{-1} 3454, 2988, 2935, 1958, 1630, 1245.

*(3aS,4S,10cR)-4-Hydroxy-2,2-dimethyl-3a,4-dihydrobenzo[b][1,3]dioxolo[4,5-e]benzofuran-5(10cH)-one (**4**)*. A stirred solution of acetonide diol **3** (20 mg, 0.072 mmol) containing tetrabutylammonium bromide (1 mg) in dry CH_2Cl_2 (2 mL) was treated with TEMPO (1 mg) and Oxone (55 mg, 0.18 mmol). The reaction mixture was stirred overnight at room temperature, concentration under reduced pressure and the crude material purified by flash column chromatography (20% EtOAc in hexane), to give hydroxy ketone **4** (17.2 mg, 86%), a white solid; R_f = 0.2 (30% EtOAc in hexane); $[\alpha]_D^{22}$ +35.0 (*c* 0.8, $CHCl_3$); HRMS (ES) calc. for $C_{15}H_{15}O_5$ $(M + H)^+$ 275.0919 found 275.0922; ^{1}H-NMR (600 MHz, $CDCl_3$): δ_H 7.85 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 8.6 Hz, 1H), 7.58 (dt, *J* = 7.2, 1.2 Hz, 1H), 7.43 (dt, *J* = 7.2, 1.0 Hz, 2H), 5.58 (d, *J* = 5.0 Hz, 1H), 4.73-4.68 (m, 1H), 3.58 (br s, 1H), 1.59 (s, 3H), 1.57 (s, 3H); ^{13}C{^{1}H}-NMR (150 MHz, $CDCl_3$): δ_C 185.4, 157.4, 146.0, 130.1, 128.1, 125.5, 124.8, 122.3, 113.1, 112.9, 81.5, 76.4, 68.4, 28.1, 26.5; IR ν_{max}/cm^{-1} 3430, 3089, 3066, 2990, 2810, 1711, 1597, 1542, 1216, 1065, 1001, 900.

*(3aS,4R,5R,10cR)-2,2-Dimethyl-3a,4,5,10c-tetrahydrobenzo[b][1,3]dioxolo[4,5-e]benzofuran-4,5-diol (**5**)*. An ice-cooled solution of hydroxyketone **4** (205 mg, 0.75 mmol) in MeOH (10 mL) was treated with sodium borohydride (57 mg, 1.5 mmol) and the mixture stirred (0.5 h) at room temperature and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL), washed with 1 M HCl (5 mL) and the aqueous washing extracted with CH_2Cl_2 (2 x 5 mL). The combined organic phase was dried ($MgSO_4$) and concentrated to afford a pure sample of *trans*-diol **5** (184 mg, 89%), a white solid; R_f = 0.2 (50% EtOAc in hexane); $[\alpha]_D^{22}$ +35.9 (*c* 1.0, $CHCl_3$); HRMS (ES) calc. for $C_{15}H_{20}NO_5$ $(M + NH_4)^+$ 294.1341 found 294.1355; ^{1}H-NMR (600 MHz, $CDCl_3$): δ_H 7.65 (d, *J* = 7.6 Hz, 1H), 7.50 (d, *J* = 8.1 Hz, 1H), 7.32 (dt, *J* = 7.5, 1.4 Hz, 1H), 7.27 (dt, *J* = 7.6, 1.0 Hz, 1H), 5.39 (d, *J* = 5.4 Hz, 1H), 4.79 (d, *J* = 5.9 Hz, 1H), 4.49 (dd, *J* = 6.9, 5.5 Hz, 1H), 4.31 (dd, *J* = 6.9, 5.9 Hz, 1H), 3.33 (br s, 1H), 2.95 (br s, 1H), 1.50 (s, 3H), 1.41 (s, 3H); ^{13}C{^{1}H}-NMR (150 MHz, $CDCl_3$): δ_C 155.9, 152.5, 126.4, 125.1, 123.4, 120.1, 111.8, 111.7, 111.6, 78.3, 74.3, 69.5, 67.6, 28.3, 26.5; IR ν_{max}/cm^{-1} 3498, 2998, 2902, 1967, 1629, 1220.

*(3aR,4S,5R,10cR)-4,5-bis((4-Methoxybenzyl)oxy)-2,2-dimethyl-3a,4,5,10c-tetrahydrobenzo[b][1,3]dioxolo[4,5-e]benzofuran (**6**)*. To a solution of *trans*-diol **5** (18 mg, 0.065 mmol) and 4-methoxybenzyl-2,2,2-trichloroacetimidate (92 mg) in toluene (4 mL) was added lanthanum (III) triflate (7.6 mg). After stirring (5 mins) the reaction mixture at room temperature, the solvent was removed under reduced pressure and the crude product purified by PLC (10% EtOAc in hexane), to furnish methoxybenzyl ether **6** (18 mg, 54%), a pale-yellow oil; R_f = 0.2 (20% EtOAc in hexane); $[\alpha]_D^{22}$ +23.6 (*c* 1.2, $CHCl_3$); HRMS (ES) calc. for $C_{31}H_{32}O_7Na$ $(M + Na)^+$ 539.2046 found 539.2048; ^{1}H-NMR (600 MHz, $CDCl_3$): δ_H 7.65 (d, *J* = 7.6 Hz, 1H), 7.50 (d, *J* = 8.2 Hz, 1H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.32 (td, *J* = 7.6 1.2 Hz, 1H) 7.29-7.25 (m, 3H), 6.90 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 1H), 5.35 (d, *J* = 5.7 Hz, 1H), 4.96 (d, *J* = 11.2 Hz, 1H), 4.80 (d, *J* = 11.2 Hz, 1H), 4.76 (d, *J* = 11.1 Hz, 1H), 4.69 (d, *J* = 11.1 Hz, 1H), 4.67 (1H, d, *J* = 5.8 Hz, 1H), 4.51 (1H, dd, *J* = 6.9, 5.8 Hz, 1H), 4.13 (dd, *J* = 6.9, 5.8 Hz, H-4), 3.82 (s, 3H), 3.80 (s, 3H), 1.50 (s, 3H), 1.40 (s, 1H); ^{13}C{^{1}H}-NMR (150 MHz, $CDCl_3$): δ_C 159.4 (4), 155.9, 153.0, 130.2 (2), 129.8, 126.5, 124.9, 123.2, 120.0, 113.8 (4), 112.2, 111.7, 111.2, 80.2, 78.2, 73.9, 72.9, 72.7, 69.3, 55.3 (2), 28.2, 26.2; IR ν_{max}/cm^{-1} 2968, 2931, 2844, 1520, 1261, 1107, 871.

*(1R,2R,3S,4R)-3,4-bis((4-Methoxybenzyl)oxy)-1,2,3,4-tetrahydrodibenzo[b,d]furan-1,2-diol (**7**)*. A solution of methoxybenzyl ether **6** (18 mg, 0.035 mmol) in THF-H_2O (4:1, 3 mL) was treated with TFA (70 µL). The reaction mixture was stirred (40 h) at 60°C, concentrated under reduced pressure, and the crude product purified by flash column chromatography (40% EtOAc in hexane), to give *cis*-diol **7** (12.5 mg, 75%), a colorless oil; R_f = 0.2 (50% EtOAc in hexane); $[\alpha]_D^{22}$ +19.0 (*c* 1.3, $CHCl_3$); HRMS (ES) calc. for $C_{28}H_{28}O_7Na$ $(M + Na)^+$ 499.1733 found 499.1732; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 7.77 (d, *J* = 7.6 Hz, 1H), 7.50 (d, *J* = 8.2 Hz, 1H), 7.35-7.30 (m, 3H), 7.27 (td, *J* = 7.7, 0.9 Hz, 1H) 7.21 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.08 (dd, *J* = 6.8, 4.2 Hz, 1H), 4.91 (d, *J* = 11.2 Hz, 1H), 4.74 (d, *J* = 11.2 Hz, 1H), 4.73 (d, *J* = 11.4 Hz, 1H), 4.70 (d, *J* = 4.7 Hz, 1H), 4.59 (d, *J* = 11.4 Hz, 1H), 4.22 (1H, dd, *J* = 7.0, 4.2 Hz, 1H), 4.03 (ddd, *J* = 10.5, 6.4, 4.2 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H); ^{13}C{^{1}H}-NMR (150 MHz, $CDCl_3$): δ_C 159.6 (2), 155.9, 151.3, 129.8 (2), 129.7, 129.6 (2), 129.4, 126.8, 125.0, 123.2, 120.9, 115.9, 114.0 (4), 111.6, 77.9, 73.5, 73.2, 72.4, 70.4, 64.3, 55.4 (2); IR ν_{max}/cm^{-1} 3996, 2954, 2917, 2849, 1575, 1542, 1249, 1089, 1011.

*(2S,3S,4R)-2-Hydroxy-3,4-bis((4-methoxybenzyl)oxy)-3,4-dihydrodibenzo[b,d]furan-1(2H)-one (**8**)*. To a stirred solution of *cis*-diol **7** (12 mg, 0.025 mmol), containing tetrabutylammonium bromide (1 mg) in dry CH_2Cl_2 (2 mL), was added TEMPO (1 mg) and Oxone™ (18 mg, 0.06 mmol). After stirring the reaction mixture, overnight at room

temperature, the solvent was removed under reduced pressure and the crude product purified by flash column chromatography (30% EtOAc in hexane), to afford *α*-hydroxyketone **8** (6.6 mg, 55%), a white solid; R_f = 0.3 (30% EtOAc in hexane); $[\alpha]_D^{22}$ +34.0 (*c* 0.7, $CHCl_3$); HRMS (ES) calc. for $C_{28}H_{26}O_7Na$ $(M + Na)^+$ 497.1576 found 497.1506; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.03 (m, 1H), 7.57 (m, 1H), 7.44-7.34 (m, 6H), 6.91 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.10 (d, *J* = 10.9 Hz, 1H), 5.01 (d, *J* = 10.7 Hz, 1H), 4.98 (d, *J* = 7.9 Hz, 1H), 4.94 (d, *J* = 10.9 Hz, 1H), 4.83 (d, *J* = 10.7 Hz, 1H), 4.45 (dd, *J* = 9.8, 1.9 Hz, 1H), 4.06 (dd, *J* = 9.8, 7.9 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.80 (d, *J* = 2.0 Hz, 1H); ^{13}C{^{1}H}-NMR (150 MHz, $CDCl_3$): δ_C 191.0, 167.4, 159.4 (2), 156.2, 130.0 (4), 129.6, 126.3, 125.1, 122.3, 122.0, 114.9, 113.9 (4), 111.9, 85.8, 77.8, 75.2, 75.1, 75.1, 74.7, 55.3 (2); IR ν_{max}/cm^{-1} 3453, 3070, 2927, 2852, 2778, 1771, 1707, 1625, 1515, 1366, 1169, 1014.

*(2S,3R,4R)-2-Methoxy-3,4-bis((4-methoxybenzyl)oxy)-3,4-dihydrodibenzo[b,d]furan-1(2H)-one (**9**)*. A glass tube, containing a mixture of *α*-hydroxyketone **8** (6.5 mg, 0.014 mmol), Ag_2O (12 mg) and MeI (10 µL) in dry THF (2 mL), was sealed under argon and the mixture stirred (24 h) at 60°C. The solvent was removed under reduced pressure and the crude product purified by flash column chromatography (15% EtOAc in hexane) to yield methyl ether **9** (4.4 mg, 66%), a colorless oil; R_f = 0.2 (20% EtOAc in hexane); $[\alpha]_D^{22}$ +47.7 (*c* 0.4, $CHCl_3$); HRMS (ES) calc. for $C_{29}H_{32}NO_7$ $(M + NH_4)^+$ 506.2179 found 506.2193; ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.06 (d, *J* = 7.2 Hz, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.43-7.28 (m, 6H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 5.05 (d, *J* = 11.1 Hz, 1H), 4.95-4.88 (m, 2H), 4.86 (d, *J* = 10.7 Hz, 1H), 4.75 (d, *J* = 10.7 Hz, 1H), 4.14 (dd, *J* = 9.3, 7.3 Hz, 1H), 3.99 (d, *J* = 9.3 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.77 (3H, s, 3H); ^{13}C{^{1}H}-NMR (150 MHz, $CDCl_3$): δ_C 190.6, 165.9, 159.6, 159.5, 156.1, 130.2, 129.9, 129.5, 126.2, 124.9, 122.8, 122.3, 115.9, 113.9, 111.7, 86.2, 83.7, 75.3, 74.8, 74.3, 61.0, 55.3; IR ν_{max}/cm^{-1} 2969, 2882, 1735, 1679, 1280, 1021, 976

(2S,3R,4R)-3,4-Dihydroxy-2-methoxy-3,4-dihydrodibenzo[b,d]furan-1(2H)-one (-)- *(Ribisin A)*.[1, 7] To a solution of methyl ether **9** (9.0 mg, 0.018 mmol) in a mixture of CH_2Cl_2 and H_2O (4:1, 2 mL) was added DDQ (12.5 mg) and the mixture stirred (18 h) at room temperature. Water (2 mL) and CH_2Cl_2 (5 mL) were added to the stirring mixture, the organic phase separated, and the remaining aqueous phase extracted with CH_2Cl_2 (5 mL). The combined organic extract was dried ($MgSO_4$), concentrated, and the residue purified by flash column chromatography (50% EtOAc in hexane) to afford (-)-ribisin A (2.9 mg, 63%), a pale-yellow solid; R_f = 0.2 (60% EtOAc in hexane); $[\alpha]_D^{22}$ -16.0 (*c* 0.2, MeOH); HRMS (ES) calc. for $C_{26}H_{24}O_{10}Na$ $(2M + Na)^+$ 519.1267 found 519.1259; ^{1}H-NMR (600 MHz, $CDCl_3$): δ_H 7.93 (dm, *J* = 7.6 Hz, 1H), 7.56 (dm, *J* = 8.1 Hz, 1H), 7.36 (dt, *J* = 7.4, 1.4 Hz, 1H), 7.32 (dt, *J* = 7.6, 1.0 Hz, 1H), 4.93 (d, *J* = 7.6 Hz, 1H), 3.97 (d, *J* = 9.9 Hz, 1H), 3.92 (dd, *J* = 9.9, 7.6 Hz, 1H), 3.66 (s, 3H); ^{13}C{^{1}H}-NMR (150 MHz, $CDCl_3$): δ_C 193.1, 169.4, 157.6, 127.2, 126.0, 124.3, 122.9, 116.1, 112.8, 87.2, 78.9, 70.4, 60.8.

(3aR,3bS,5S,6aS,11cR)-5-(4-Methoxyphenyl)-2,2-imethyl-3a,3b,6a,11c-tetrahydrobenzo[4',5']furo[2',3':5,6]benzo[1,2-d:3,4-d']bis([1,3]dioxole) and *(3aR,3bS,5R,6aS,11cR)-5-(4-methoxyphenyl)-2,2-Dimethyl-3a,3b,6a,11c-tetrahydrobenzo[4',5']furo[2',3':5,6]benzo[1,2-d:3,4-d']bis([1,3]dioxole) (**10a** and **10b**)*. To an ice-cooled solution of *cis*-diol **3** (40 mg, 0.145 mmol) and anisaldehyde dimethyl acetal (0.10 mL) in dry CH_2Cl_2 (3 mL) was added (+)-10-camphorsulfonic acid (14 mg). The reaction mixture was stirred (3 h) at 0°C, warmed to room temperature and treated with saturated aqueous solution of $NaHCO_3$ (2 mL). The organic phase was separated, the remaining aqueous solution extracted with CH_2Cl_2 (2 x 3 mL), and the combined organic solution dried ($MgSO_4$) and concentrated. The resulting yellow oil was purified by flash column chromatography (8% EtOAc in hexane) to give a mixture of acetals *exo* **10a** and *endo* **10b** (57:43), a pale-yellow oil (50 mg, 87%); R_f = 0.2 (5% EtOAc in hexane); HRMS (ES) calc. for $C_{23}H_{22}O_6Na$ $(M + Na)^+$ 417.1314 found 417.1309; Minor *endo*-diastereoisomer **10b**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 7.74 (dm, *J* = 6.9 Hz, 1H), 7.51 (dm, *J* = 7.1 Hz, 1H), 7.40-7.27 (m, 9H,), 7.14 (d, *J* = 8.7 Hz, 2 H), 6.76 (d, *J* = 8.7 Hz, 2H), 6.02 (s, 1H), 5.44 (d, *J* = 5.1 Hz, 1H), 5.39 (d, *J* = 6.5 Hz, 1H), 5.01 (dd, *J* = 6.5, 2.8 Hz, 1H), 4.91 (dd, *J* = 5.1, 2.8 Hz, 1H), 3.72 (s, 3H), 1.46 (s, 3H), 1.12 (s, 3H). Major *exo*-diastereoisomer **10a**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 7.76 (dm, *J* = 7.3 Hz, 1H), 7.54 (dm, *J* = 7.7 Hz, 1H), 7.39 (d, *J* = 8.7 Hz, 2 H), 7.37-7.27 (m, 9H), 5.70 (s, 1H), 5.62 (d, *J* = 5.8 Hz, 1H), 5.51 (d, *J* = 4.9 Hz, 1H), 5.01 (dd, *J* = 5.8, 3.0 Hz, 1H), 4.91 (dd, *J* = 5.0, 3.0 Hz, 1H), 3.81 (s, 3H), 1.45 (s, 3H), 1.09 (s, 3H).

*(3aS,4S,5S,10cR)-5-((4-Methoxybenzyl)oxy)-2,2-dimethyl-3a,4,5,10c-tetrahydrobenzo[b][1,3]dioxolo[4,5-e]benzofuran-4-ol (**11**) and (3aR,4R,5S,10cR)-4-((4-Methoxybenzyl)oxy)-2,2-dimethyl-3a,4,5,10c-tetrahydrobenzo[b][1,3]dioxolo[4,5-e]benzofuran-5-ol (**12**)*. To a solution of *cis*-diol **3** (120 mg, 0.43 mmol) and (+)-camphorsulfonic acid (40 mg), in dry CH_2Cl_2 (5 mL) maintained at -15°C, was added 1-(dimethoxymethyl)-4-methoxybenzene (0.30 mL, 1.6 mmol). After stirring (4 h) the reaction mixture it was diluted with CH_2Cl_2 (10 mL), allowed to warm up to room temperature and washed with a saturated aqueous solution of $NaHCO_3$ (10 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to give a mixture of diastereomers **10a** and **10b**. This was taken up in dry CH_2Cl_2 (10 mL), cooled to -78°C and treated with a solution of DIBAL (1 M, 4.3 mL) in hexane. The mixture was stirred (6 h) at -78°C, allowed to warm to room temperature, and a saturated aqueous solution of potassium sodium tartrate (2 mL) was added. After stirring the reaction mixture overnight, the organic phase was separated and the remaining aqueous phase extracted with CH_2Cl_2 (5 mL). The combined organic extract was dried ($MgSO_4$) and concentrated. The crude product obtained was purified by flash column chromatography (25% EtOAc in hexane) to give benzylic ether **11**, a pale-yellow solid, and homobenzylic ether **12**, a pale-yellow oil.

Benzylic ether **11** (52 mg, 30%); R_f = 0.2 (30% EtOAc in hexane); $[\alpha]_D^{22}$ +8.4 (*c* 1.5, $CHCl_3$); HRMS (ES) calc. for $C_{23}H_{28}NO_6$ $(M + NH_4)^+$ 414.1917 found 414.1928; ^{1}H-NMR (600 MHz, $CDCl_3$): δ_H 7.65 (d, *J* = 3.9 Hz, 1H), 7.48 (m, 1H), 7.32 (m, 2H), 7.30 (m, 1H), 7.26 (m, 1H), 6.89 (m, 2H), 5.39 (d, *J* = 5.6 Hz, 1H), 4.91 (t, *J* = 4.3 Hz, 1H), 4.82 (d, *J* = 11.7 Hz, 1H), 4.72 (d, *J* = 11.7 Hz, 1H), 4.66 (dd, *J* = 7.3, 5.6 Hz, 1H), 4.02 (dd, *J* = 7.3, 4.0 Hz, 1H), 3.80 (s, 3H), 2.83 (d, *J* = 4.8 Hz, 1H), 1.50 (s, 3H), 1.33 (s, 3H); ^{13}C{^{1}H}-NMR (150

MHz, $CDCl_3$): δ_C 159.7, 155.9, 152.0, 129.8, 129.6, 128.9, 126.4, 125.1, 123.3, 120.1, 114.1, 111.7, 110.8, 78.2, 75.8, 73.0, 69.6, 62.9, 55.3, 28.1, 26.3; IR ν_{max}/cm^{-1} 2957, 2924, 2853, 1637, 1080, 1034, 923.

Homobenzyl ether **12** (27 mg, 16%); R_f = 0.2 (30% EtOAc in hexane); $[\alpha]_D^{22}$-8.2 (*c* 0.9, $CHCl_3$); HRMS (ES) calc. for $C_{23}H_{28}NO_6$ $(M + NH_4)^+$ 414.1917 found 414.1928; ^{1}H-NMR (600 MHz, $CDCl_3$): δ_H 7.69 (d, *J* = 7.5 Hz, 1H), 7.52 (d, *J* = 8.3 Hz, 1H), 7.35 (dt, *J* = 7.3, 1.2 Hz, 1H), 7.32 (d, *J* = 8.6 Hz, 2H), 7.29 (dt, *J* = 7.5, 1.0 Hz, 1H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.42 (d, *J* = 5.7 Hz, 1H), 4.84 (d, *J* = 11.2 Hz, 1H), 4.74 (*d*, J = 4.1 Hz, 1H), 4.71 (d, *J* = 11.2 Hz, 1H), 4.57 (dd, *J* = 7.7, 5.8 Hz, 1H), 4.19 (td, *J* = 7.5, 4.0 Hz, 1H), 3.81 (s, 3H), 2.64 (d, *J* = 7.5 Hz, 1H), 1.51 (s, 3H), 1.43 (s, 3H); ^{13}C{^{1}H}-NMR (150 MHz, $CDCl_3$): δ_C 159.6, 155.9, 152.2, 129.8, 129.4, 126.5, 125.3, 123.4, 120.3, 114.0, 113.6, 111.7, 110.8, 77.6, 72.3, 71.5, 70.3, 69.5, 55.3, 28.2, 26.2; IR ν_{max}/cm^{-1} 2958, 2925, 2853, 1641, 1080, 1012, 907.

A small portion of the minor diastereoisomer **10b** was separated from the acetal mixture **10a**/**10b** by multiple elution PLC. This sample on similar DIBAL reduction gave exclusively isomer **12**.

*(3aR,4S,5S,10cR)-4-Methoxy-5-((4-methoxybenzyl)oxy)-2,2-dimethyl-3a,4,5,10c-tetrahydrobenzo[b][1,3]dioxolo[4,5-e]benzofuran (**13**).* To a solution of alcohol **11** (16 mg, 0.040 mmol) in dry THF (4 mL) was added sodium hydride (5 mg), under an argon atmosphere, followed by the addition of methyl iodide (12 µL). The reaction mixture was stirred (4 h) at room temperature, the solvent removed under reduced pressure, and the crude product purified by flash column chromatography (10% EtOAc-hexane), to afford methyl ether **13** (14.9 mg, 90%), colorless oil; R_f = 0.2 (20% EtOAc in hexane); $[\alpha]_D^{22}$ -95.6 (*c* 0.5, $CHCl_3$); HRMS (ES) calc. for $C_{24}H_{30}NO_6$ $(M + NH_4)^+$ 428.2073 found 428.2052; ^{1}H-NMR (600 MHz, $CDCl_3$): δ_H 7.68 (d, *J* = 7.7 Hz, 1H), 7.51 (d, *J* = 8.2 Hz, 1H), 7.37 (d, *J* = 8.8 Hz, 2H), 7.34 (dt, *J* = 7.3, 1.3 Hz, 8H), 7.29 (dt, *J* = 7.61.0 Hz, 9H), 6.89 (d, *J* = 8.6 Hz, 1H), 5.43 (d, *J* = 6.2 Hz, 1H), 4.81 (d, *J* = 3.6 Hz, 1H), 4.75 (d, *J* = 11.7 Hz, 1H), 4.74 (dd, *J* = 8.5, 6.2 Hz, 1H), 4.68 (d, *J* = 11.7 Hz, 1H), 3.80 (s, 3H), 3.67 (dd, *J* = 8.5, 3.6 Hz, 1H), 3.48 (s, 3H), 1.52 (s, 3H), 1.49 (s, 3H); ^{13}C{^{1}H}-NMR (150 MHz, $CDCl_3$): δ_C 159.4, 155.9, 152.9, 129.9, 129.8, 126.4, 125.2, 123.4, 120.4, 113.8, 113.4, 111.7, 110.7, 81.6, 76.1, 71.7, 69.4, 66.9, 58.1, 55.3, 28.2, 25.8; IR ν_{max}/cm^{-1} 2956, 2924, 2854, 1514, 1249, 1109, 874.

*(1R,2R,3S,4S)-3-Methoxy-4-((4-methoxybenzyl)oxy)-1,2,3,4-tetrahydrodibenzo[b,d]furan-1,2-diol (**14**).* A solution of methyl ether **13** (8.0 mg, 0.020 mmol) in THF-H_2O (9:1, 2 mL) was treated with TFA (10 µL). The reaction mixture was stirred (50°C) overnight, concentrated under reduced pressure, and the product purified by flash column chromatography (60% EtOAc in hexane), to yield *cis*-diol **14** (7.0 mg, 97%), colorless oil; R_f = 0.2 (60% EtOAc-hexane); $[\alpha]_D^{22}$ -139.0 (*c* 0.7, $CHCl_3$); HRMS (ES) calc. for $C_{21}H_{22}O_6Na$ $(M + Na)^+$ 393.1314 found 393.1302; ^{1}H-NMR (600 MHz, $CDCl_3$): δ_H 7.68 (d, *J* = 7.7 Hz, 1H), 7.51 (d, *J* = 8.2 Hz, 1H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.34 (dt, *J* = 7.3, 1.3 Hz, 1H), 7.28 (dt, *J* = 7.6, 1.0 Hz, 1H), 6.90 (d, *J* = 8.6 Hz, 2H), 5.16 (d, *J* = 4.2 Hz, 1H), 4.84 (d, *J* = 3.9 Hz, 1H), 4.80 (d, *J* = 11.7 Hz, 1H), 4.74 (d, *J* = 11.7 Hz, 1H), 4.37 (dd, *J* = 10.2, 3.9 Hz, 1H), 3.81 (s, 3H), 3.78 (dd, *J* = 10.1, 3.9 Hz, 1H), 3.39 (s, 3H), 3.22 (br s, 2H); ^{13}C{^{1}H}-NMR (150 MHz, $CDCl_3$): δ_C 159.5, 156.0, 152.4, 130.2, 129.6, 126.4, 125.2, 123.3, 120.1, 116.0, 113.9, 111.7, 78.1, 71.7, 68.3, 65.9, 62.5, 57.2, 55.3; IR ν_{max}/cm^{-1} 3998, 2955, 2917, 2849, 1576, 1382, 1222, 1033, 751.

*(2S,3S,4S)-2-Hydroxy-3-methoxy-4-((4-methoxybenzyl)oxy)-3,4-dihydrodibenzo[b,d]furan-1(2H)-one (**15**).* TEMPO (1 mg) and Oxone™ (28 mg, 0.09 mmol) were sequentially added to a stirred solution of *cis*-diol **14** (15 mg, 0.041 mmol) and tetrabutylammonium bromide (2 mg) in dry CH_2Cl_2 (4 mL). After stirring the reaction mixture, overnight at room temperature, it was concentrated under reduced pressure, and the residue purified by flash column chromatography (50% EtOAc in hexane) to afford ketone **15** (12.8 mg, 86%), a pale-yellow oil; R_f = 0.3 (50% EtOAc in hexane); $[\alpha]_D^{22}$ -118.0 (*c* 1.0, $CHCl_3$); HRMS (ES) calc. for $C_{21}H_{20}O_6Na$ $(M + Na)^+$ 391.1158 found 391.1155; ^{1}H-NMR (600 MHz, $CDCl_3$): δ_H 8.08 (dm, 1H), 7.58 (m, 1H), 7.44 (td, *J* = 7.3, 1.5 Hz, 1H), 7.42-7.38 (m, 3H), 6.91 (d, *J* = 8.7 Hz, 2H), 5.04 (d, *J* = 3.8 Hz, 1H), 4.88 (dd, *J* = 9.9, 1.0 Hz, 1H), 4.83 (d, *J* = 11.7 Hz, 1H), 4.80 (d, *J* = 11.7 Hz, 1H), 3.81 (s, 3H), 3.72 (dd, *J* = 9.9, 3.7 Hz, 1H), 3.59 (d, *J* = 1.2 Hz, 1H), 3.54 (3H, s, 3H); ^{13}C{^{1}H}-NMR (150 MHz, $CDCl_3$): δ_C191.5, 165.9, 159.4, 156.2, 130.1 (2), 129.1, 126.7, 125.3, 122.5 (2), 116.1, 114.0 (2), 111.9, 83.1, 73.6, 72.5, 67.4, 58.2, 55.4; IR ν_{max}/cm^{-1} 3844, 3681, 2948, 2880, 1652, 1410, 1128, 1044, 852.

*(2S,3R,4S)-2,3-Dimethoxy-4-((4-methoxybenzyl)oxy)-3,4-dihydrodibenzo[b,d]furan-1(2H)-one (**16**).* Following the procedure described for the synthesis of methyl ether **9**, a mixture of ketone **15** (9.2 mg, 0.025 mmol), Ag_2O (8.0 mg) and MeI (10 µL) in dry THF (2 mL) was heated in a sealed tube under argon atmosphere. The crude product obtained was purified by flash column chromatography (20% EtOAc in hexane) to give dimethoxy ketone **16** (7.3 mg, 76%), colorless oil; R_f = 0.2 (30% EtOAc in hexane); $[\alpha]_D^{22}$ -139.0 (*c* 0.7, $CHCl_3$); HRMS (ES) calc. for $C_{22}H_{23}O_6$ $(M + H)^+$ 383.1495 found 383.1471; ^{1}H-NMR (600 MHz, $CDCl_3$): δ_H 8.09 (dm, *J* = 7.7 Hz, 1H), 7.55 (m, 1H), 7.43-7.35 (m, 4H), 6.92 (d, *J* = 8.7 Hz, 2H), 5.05 (d, *J* = 3.8 Hz, 1H), 4.88 (d, *J* = 11.8 Hz, 1H), 4.80 (d, *J* = 11.8 Hz, 1H), 4.31 (d, *J* = 8.5 Hz, 1H), 3.98 (dd, *J* = 8.4, 3.7 Hz, 1H), 3.82 (s, 3H), 3.70 (s, 3H), 3.52 (s, 3H); ^{13}C{^{1}H}-NMR (150 MHz, $CDCl_3$): δ_C 190.9, 165.3, 159.6, 155.9, 130.0, 129.3, 126.2, 125.0, 123.1, 122.5, 116.4, 114.0, 111.7, 82.5, 81.9, 72.6, 68.7, 60.5, 59.0, 55.4; IR ν_{max}/cm^{-1} 2947, 2880, 1739, 1684, 1484, 1281, 1041.

(2S,3R,4S)-4-Hydroxy-2,3-dimethoxy-3,4-dihydrodibenzo[b,d]furan-1(2H)-one [(–)-Ribisin B]. [1, 7]

Following the procedure described for the last step in the literature synthesis of (–)-ribisin A, a solution of dimethoxy ketone **16** (7.6 mg, 0.020 mmol) in CH_2Cl_2 and H_2O (4:1, 2 mL) was reacted with DDQ (5 mg). Purification of the crude product by flash column chromatography (25% EtOAc in hexane) furnished (–)-ribisin B (4.0 mg, 77%), as a colorless oil; R_f = 0.2 (30% EtOAc in hexane); $[\alpha]_D^{22}$ -25.8 (*c* 0.4, $CHCl_3$); HRMS (ES) calc. for $C_{14}H_{15}O_5$ $(M + H)^+$ 263.0919 found 263.0912; ^{1}H-NMR (600 MHz, $CDCl_3$): δ_H 8.08 (dm, *J* = 7.6 Hz, 1H), 7.56 (dm, *J* = 7.7 Hz, 1H), 7.41-7.35 (m, 2H), 5.30 (dd, *J* = 7.1, 4.2 Hz, 1H), 4.15 (d, *J* = 6.7 Hz, 1H), 4.01 (dd, *J* = 6.7, 4.2 Hz, 1H), 3.62 (s, 3H), 3.61 (s, 3H), 3.05 (d, *J* = 7.1 Hz, 1H); ^{13}C{^{1}H}-NMR (150 MHz, $CDCl_3$): δ_C 190.2, 165.2, 155.8, 126.1, 124.9, 123.1, 122.3, 115.3, 111.8, 81.9, 81.7, 63.8, 59.8, 59.5.

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Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra are presented for all intermediates.

REFERENCES

1. Liu, Y. H.; Kubo, M.; Fukuyama, Y., Nerve Growth Factor-Potentiating Benzofuran Derivatives from the Medicinal Fungus *Phellinus ribis*. *J. Nat. Prod.* **2012**, *75*, 2152-7.
2. Liu, Y. H.; Wang, F. S., Structural characterization of an active polysaccharide from *Phellinus ribis*. *Carbohydr. Polym.* **2007**, *70*, 386-92.
3. Lee, I. K.; Lee, J. H.; Yun, B. S., Polychlorinated compounds with PPAR-gamma agonistic effect from the medicinal fungus *Phellinus ribis*. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4566-8.
4. Kubo, M.; Liu, Y. H.; Ishida, M.; Harada, K.; Fukuyama, Y., A New Spiroindene Pigment from the Medicinal Fungus Phellinus ribis. *Chem. Pharm. Bull.* **2014**, *62*, 122-4.
5. Zhang, C. L.; Liu, J.; Du, Y. G., Total synthesis of ribisin A. *Tetrahedron Lett.* **2014**, *55*, 959-61.
6. Lan, P.; Banwell, M. G.; Ward, J. S.; Willis, A. C., Chemoenzymatic Total Synthesis and Reassignment of the Absolute Configuration of Ribisin C. *Org. Lett.* **2014**, *16*, 228-31.
7. Lan, P.; Banwell, M. G.; Willis, A. C., Chemoenzymatic Total Syntheses of Ribisins A, B, and D, Polyoxygenated Benzofuran Derivatives Displaying NGF-Potentiating Properties. *J. Org. Chem.* **2014**, *79*, 2829-42.
8. Boyd, D. R.; Sharma, N. D.; Harrison, J. S.; Malone, J. F.; McRoberts, W. C.; Hamilton, J. T. G.; Harper, D. B., Enzyme-catalysed synthesis and reactions of benzene oxide/oxepine derivatives of methyl benzoates. *Org. Biomol. Chem.* **2008**, *6*, 1251-9.
9. Min, K. L.; Kim, Y. H.; Kim, Y. W.; Jung, H. S.; Hah, Y. C., Characterization of a novel laccase produced by the wood-rotting fungus Phellinus ribis. *Arch. Biochem. Biophys.* **2001**, *392*, 279-86.
10. Tang, F.; Lan, P.; Bolte, B.; Banwell, M. G.; Ward, J. S.; Willis, A. C., Total Synthesis of (+)-Viridianol, a Marine-Derived Sesquiterpene Embodying the Decahydrocyclobuta d indene Framework. *J. Org. Chem.* **2018**, *83*, 14049-56.
11. Dlugosch, M.; Banwell, M. G., Synthesis of a Highly Functionalised and Homochiral 2-Iodocyclohexenone Related to the C-Ring of the Polycyclic, Indole Alkaloids Aspidophytine and Haplophytine. *Aust. J. Chem.* **2018**, *71*, 573-9.
12. Dlugosch, M.; Ma, X. H.; Yang, S. X.; Banwell, M. G.; Ma, C. X.; Ward, J. S.; Carr, P., Syntheses of Structurally and Stereochemically Varied Forms of C_7N Aminocyclitol Derivatives from Enzymatically Derived and Homochiral *cis*-1,2-Dihydrocatechols. *Org. Lett.* **2018**, *20*, 7225-8.
13. Baidilov, D.; Rycek, L.; Trant, J. F.; Froese, J.; Murphy, B.; Hudlicky, T., Chemoenzymatic Synthesis of Advanced Intermediates for Formal Total Syntheses of Tetrodotoxin. *Angew. Chem., Int. Ed.* **2018**, *57*, 10994-8.
14. Borra, S.; Kumar, M.; McNulty, J.; Baidilov, D.; Hudlicky, T., Chemoenzymatic Synthesis of the Antifungal Compound (-)-Pestynol by a Convergent, Sonogashira Construction of the Central Yne-Diene. *Eur. J. Org. Chem.* **2019**, 77-9.
15. Borra, S.; Lapinskaite, R.; Kempthorne, C.; Liscombe, D.; McNulty, J.; Hudlicky, T., Isolation, Synthesis, and Semisynthesis of Amaryllidaceae Constituents from Narcissus and Galanthus sp.: De Novo Total Synthesis of 2-*epi*-Narciclasine. *J. Nat. Prod.* **2018**, *81*, 1451-9.
16. Endoma-Arias, M. A. A.; Makarova, M.; Dela Paz, H. E.; Hudlicky, T., Chemoenzymatic Total Synthesis of (+)-Oxycodone from Phenethyl Acetate. *Synthesis-Stuttgart* **2019**, *51*, 225-32.
17. Hudlicky, T., Benefits of Unconventional Methods in the Total Synthesis of Natural Products. *Acs Omega* **2018**, *3*, 17326-40.
18. Lewis, S. E., Applications of biocatalytic arene *ipso*, *ortho cis*-dihydroxylation in synthesis. *Chem. Commun.* **2014**, *50*, 2821-30.
19. Lewis, S. E., Asymmetric Dearomatisation Under Enzymatic Conditions. In *Asymmetric Dearomatisation Reactions*, You, S. L., Ed. Wiley-VCH: Weinheim, 2016; pp 279-346.
20. Boyd, D. R.; Sharma, N. D.; Carroll, J. G.; Loke, P. L.; O'Dowd, C. R.; Allen, C. C. R., Biphenyl dioxygenase-catalysed *cis*-dihydroxylation of tricyclic azaarenes: chemoenzymatic synthesis of arene oxide metabolites and furoquinoline alkaloids. *RSC Adv.* **2013**, *3*, 10944-55.
21. Resnick, S. M.; Gibson, D. T., Regio- and stereospecific oxidation of fluorene, dibenzofuran, and dibenzothiophene by naphthalene dioxygenase from Pseudomonas sp strain NCIB 9816-4. *Appl. Environ. Microbiol.* **1996**, *62*, 4073-80.
22. Cerniglia, C. E.; Morgan, J. C.; Gibson, D. T., Bacterial and Fungal Oxidation of

Dibenzofuran. *Biochem. J.* **1979**, *180*, 175-85.
23. Bianchi, D.; Bosetti, A.; Cidaria, D.; Bernardi, A.; Gagliardi, I.; Damico, P., Oxidation of polycyclic aromatic heterocycles by Pseudomonas fluorescens TTC1. *Appl. Microbiol. Biotechnol.* **1997**, *47*, 596-9.
24. Boyd, D. R.; Sharma, N. D.; Malone, J. F.; McIntyre, P. B. A.; Stevenson, P. J.; Allen, C. C. R.; Kwit, M.; Gawronski, J., Structure, stereochemistry and synthesis of enantiopure cyclohexenone *cis*-diol bacterial metabolites derived from phenols. *Org. Biomol. Chem.* **2012**, *10*, 6217-29.
25. Boyd, D. R.; Sharma, N. D.; Malone, J. F.; McIntyre, P. B. A.; McRoberts, C.; Floyd, S.; Allen, C. C. R.; Gohil, A.; Coles, S. J.; Horton, P. N.; Stevenson, P. J., Toluene Dioxygenase-Catalyzed Synthesis and Reactions of *cis*-Diol Metabolites Derived from 2-and 3-Methoxyphenols. *J. Org. Chem.* **2015**, *80*, 3429-39.
26. Boyd, D. R.; Sharma, N. D.; McIntyre, P. B. A.; Stevenson, P. J.; McRoberts, W. C.; Gohil, A.; Hoering, P.; Allen, C. C. R., Enzyme-Catalysed Synthesis of Cyclohex-2-en-1-one *cis*-Diols from Substituted Phenols, Anilines and Derived 4-Hydroxycyclohex-2-en-1-ones. *Adv. Synth. Catal.* **2017**, *359*, 4002-14.
27. Boyd, D. R.; Sharma, N. D.; Brannigan, I. N.; McGivern, C. J.; Nockemann, P.; Stevenson, P. J.; McRoberts, C.; Hoering, P.; Allen, C. C. R., *Cis*-Dihydroxylation of Tricyclic Arenes and Heteroarenes Catalyzed by Toluene Dioxygenase: A Molecular Docking Study and Experimental Validation. *Adv. Synth. Catal.* **2019**, *361*, 2526-37.
28. Vanrheenen, V.; Kelly, R. C.; Cha, D. Y., Improved Catalytic OsO_4 Oxidation of Olefins to *cis*-1,2-Glycols using Tertiary Amine Oxides as Oxidant. *Tetrahedron Lett.* **1976**, 1973-6.
29. Bolm, C.; Magnus, A. S.; Hildebrand, J. P., Catalytic synthesis of aldehydes and ketones under mild conditions using TEMPO/Oxone. *Organic Letters* **2000**, *2*, 1173-5.
30. Hudlicky, T.; Fan, R. L.; Tsunoda, T.; Luna, H.; Andersen, C.; Price, J. D., Biocatalysis as a Rational Approach to Enantiodivergent Synthesis of Highly Oxygenated Compounds - (+)-Pinitol and (-)-Pinitol and Other Cyclitols. *Isr. J. Chem.* **1991**, *31*, 229-38.
31. Heravi, M. M.; Zadsirjan, V.; Hamidi, H.; Amiri, P. H. T., Total synthesis of natural products containing benzofuran rings. *RSC Adv.* **2017**, *7*, 24470-521.
32. Oliveira, A.; Oliveira-Campos, A. M. F.; Raposo, M. M. M.; Griffiths, J.; Machado, A. E. H., Fries rearrangement of dibenzofuran-2-yl ethanoate under photochemical and Lewis-acid-catalysed conditions. *Tetrahedron* **2004**, *60*, 6145-54.