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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 the 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 major 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 reaction.

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 or heart 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 to ribisin A was to use a Ferrier rearrangement of an enol ether, derived from α -D-glucopyranose, with all three stereocentres of the correct absolute configuration.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 stereochemistry for ribisin C and the relative stereochemistry for ribisin B, where two out of the three stereocentres had to be re-assigned. 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

Figure 1. Examples of natural products containing dibenzofuran subunits (Scheme 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 dibenzofuran precursor (Scheme 1) prompted the current chemoenzymatic approach to ribisins A and B from dibenzofuran.

Scheme 1. Proposed biosynthetic route to ribisins A and B from 2-hydroxycinnamic acid and a dibenzofuran 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 chiral 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 a mutant strain of the soil bacterium *P. putida* UV4 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, dibenzothi-

ophene 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 required four oxygen atoms to the metabolite in a stereocontrolled manner. This method 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 *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 found to be enantiopure (>98% *ee*) and was ideally functionalized for conversion to ribisins A and B.

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 steric inhibition 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 achieved in two steps, by a chemoselective oxidation of the more activated alcohol of diol **3** to form α -hydroxyketone **4**, followed by a stereoselective reduction to give *trans*-diol **5**. Although a number of methods were 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 free radical catalyst (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 (Ag₂O/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, regioselective *O*-methylation and alcohol oxidation to form a ketone were required.

Reaction of diol **3** with 1-(dimethoxymethyl)-4-methoxybenzene formed a 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's were not observed and, therefore, the relative stereochemistry at the acetal stereocentre of isomers **10a** and **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. It indicates that the *p*-methoxyphenyl group of the minor acetal isomer **10b** is pseudoaxial and proximate to the C-10c proton. This premise was tentatively used to assign the absolute configuration at the acetal centre. 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.

After careful multiple elution PLC, only the minor 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 a major proportion 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).

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, H₂O), in a similar manner to that used for acetonide **6** (Scheme 2), to form *cis*-diol **14** (97% yield). The C-1 hydroxyl group of diol **14** was chemoselectively oxidized to ketone **15** (catalytic TEMPO with Oxone, Scheme 3) (86% yield). Methylation (Ag₂O/MeI) of the α -hydroxy ketone **15** gave dimethoxy ketone **16** (76% yield). Finally, the PMB protecting group was oxidatively removed (DDQ, CH₂Cl₂) from PMB-ether **16** to furnish (-)-ribisin B (77% yield) giving a 10% overall yield from *cis*-dihydrodiol **1** over nine steps.

As part of an earlier study of biotransformations (*P. putida* UV4) of tricyclic heteroarenes, the isolation of *cis*-dihydrodiol metabolite **1**, and its potential as a chiral synthon, was demonstrated by the synthesis and absolute configuration stereochemical assignment of diol epoxide **18**, following treatment of a bromohydrin intermediate **17** with sodium methoxide (Scheme 4).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 herein (Scheme 4). Despite these changes in reaction conditions neither triol was obtained. Reactions of unactivated diol epoxides toward nucleophilic attack had been reported by using Al₂O₃ 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 intermediate **4**, is currently under investigation as a chiral precursor.

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 the chiral dibenzofuran derivatives, 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

NMR spectra were recorded on Bruker AV-400 and AV-600 instruments using specified solvents. Chemical shifts (δ) are reported in ppm relative to SiMe₄ and coupling constants (J) are given in Hertz (Hz). Optical rotations ($[\alpha]_D$) measurements (10⁻¹ deg cm² g⁻¹) were carried out at ambient temperature on a Perkin-Elmer 214 polarimeter and specified solvent concentration (g /100 mL) at 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. Accurate molecular weights were obtained by the peak matching method, using heptacosafuorotributylamine as the standard reference, and were accurate to within $\pm 5 \times 10^{-6}$ a.m.u. Melting points were recorded in degrees Celsius using a Stuart SMP10 melting point apparatus. Merck Kieselgel 60F₂₅₄ analytical plates were used for TLC analyses. Preparative layer chromatography (PLC) separations were carried out on glass plates (20 cm x 20 cm) coated with Merck Kieselgel PF_{254/366} silica gel (21 g silica gel in 62 mL water). Flash column chromatography was performed on Fluorochem silicagel 60A 40-63u.

(1*R*,2*S*)-1,2-Dihydrodibenzo[*b,d*]furan-1,2-diol (**1**).^{21, 27}

Glucose (10 g) was added to a 2000 mL baffled Erlenmeyer flask containing 500 mL of MSM culture medium, before inoculation with *P. putida* UV4. The contents were shaken at 140 rpm, at 30°C for 24 h. Dibenzo-furan (250 mg, 1.49 mmol) and glucose (2 g) were added to the mixture and it was incubated at 30°C (pH 7.5 - 8) on an orbital shaker (140 rpm) for 24 - 48 h, with further addition of glucose (2 g) after 24 h. The cells were removed by centrifugation (7000 rpm, 15 mins) and the supernatant was concentrated *in vacuo* to ca. 50 mL before extraction with EtOAc (3 x 75 mL). The combined organic extracts were concentrated to give diol **1** as a white crystalline solid (252 mg, 84%); mp 96-98°C (EtOAc/hexane); R_f = 0.25 (30% EtOAc in hexane); $[\alpha]_D$ +200.0 (c 0.8, CHCl₃); HRMS (ES) calcd for C₁₂H₁₀O₃Na (M + Na)⁺ 225.0522 found 225.0502; ¹H-NMR (400 MHz, CDCl₃): δ 7.62 (m, 1H), 7.45 (m, 1H), 7.27 (m, 2H), 6.51 (dd, J = 10.0, 2.3 Hz, 1H), 6.05 (ddd, J = 10.0, 2.5, 0.7 Hz, 1H), 4.96 (dd, J = 6.3, 0.7 Hz, 1H), 4.67 (dt, J = 6.3, 2.5 Hz, 1H), 2.48 (br s, 2 H); ¹³C-NMR (100 MHz, CDCl₃): δ 155.1, 152.0, 134.3, 126.5, 124.6, 123.6, 119.2, 117.4, 113.5, 111.7, 70.8, 65.1. Spectroscopic data matched literature values.

(3*aR*,10*cS*)-2,2-Dimethyl-3*a*,10*c*-dihydrobenzo[*b*][1,3]dioxolo[4,5-*e*]benzofuran (**2**).²² To a stirring 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 (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 NaHCO₃ (5 mL), the mixture was concentrated under reduced pressure and the concentrate extracted with EtOAc (2 x 15 mL). The organic phase was dried (Na₂SO₄), concentrated and the crude product purified by flash column chromatography (4% EtOAc in hexane), to afford acetone **2**, a white solid, (237 mg, 73%); R_f = 0.45 (10% EtOAc in hexane); $[\alpha]_D$ +130.8 (c 0.66, CHCl₃); HRMS (ES) calcd for C₁₅H₁₄O₃Na (M + Na)⁺ 265.0836 found 265.0841; ¹H-NMR (400 MHz, CDCl₃): 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 (3H, s, Me), 1.38 (3H, s, Me); ¹³C-NMR (100 MHz, CDCl₃): 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 $\nu_{\max}$ /cm⁻¹ 2068, 1935, 1446. ¹H NMR data was in good agreement with literature values.

The decomposition 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 ¹H-NMR (400 MHz, CDCl₃) 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); ¹³C-NMR (100 MHz, CDCl₃) 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.

(3*aS*,4*R*,5*S*,10*cR*)-2,2-Dimethyl-3*a*,4,5,10*c*-tetrahydrobenzo[*b*][1,3]dioxolo[4,5-*e*]benzofuran-4,5-diol (**3**). To a stirred solution of acetone **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 ^tBuOH (2.5 wt %, 70 μ L). After stirring the reaction mixture overnight at room temperature, a saturated aqueous solution of Na₂S₂O₅ (1 mL) was added to it and the stirring continued for another 10 mins. The reaction mixture was concentrated *in vacuo*, water (2 mL) added to it, the mixture thoroughly extracted with EtOAc (2 x 5 mL) and the organic extract was dried (Na₂SO₄) 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 = 0.18 (40% EtOAc in hexane); $[\alpha]_D$ +30.6 (c 0.36, MeOH); HRMS (ES) calcd for C₁₅H₁₆O₅Na (M + Na)⁺ 299.0887 found 299.0895; ¹H-NMR (400 MHz, CDCl₃): δ 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 (3H, s, Me), 1.41 (3H, s, Me). ¹³C-NMR (100 MHz, CDCl₃): δ 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 $\nu_{\max}$ /cm⁻¹ 3454, 2988, 2935, 1958, 1630, 1245.

(3*aS*,4*S*,10*cR*)-4-Hydroxy-2,2-dimethyl-3*a*,4-dihydrobenzo[*b*][1,3]dioxolo[4,5-*e*]benzofuran-5(10*cH*)-one (**4**). A stirred solution of acetone **2** (20 mg, 0.072 mmol) containing tetrabutylammonium bromide (1 mg) in dry CH₂Cl₂ (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 0.21 (30% EtOAc in hexane); $[\alpha]_D$ +35.0 (c 0.8, CHCl₃); HRMS (ES) calcd for C₁₅H₁₅O₅ (M + H)⁺ 275.0919 found 275.0922; ¹H-NMR (600 MHz, CDCl₃): δ 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, Me), 1.57 (s, Me); ¹³C-NMR (150 MHz, CDCl₃): δ 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 $\nu_{\max}$ /cm⁻¹ 3430, 3089, 3066, 2990, 2810, 1711, 1597, 1542, 1216, 1065, 1001, 900.

(3*aS*,4*R*,5*R*,10*cR*)-2,2-Dimethyl-3*a*,4,5,10*c*-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. The concentrate obtained after removal of solvent was dissolved in CH₂Cl₂ (20 mL), washed with 1 M HCl (5 mL) and the aqueous washing extracted with CH₂Cl₂ (2 x 5 mL). The combined organic phase was dried (MgSO₄) and concentrated to afford a pure sample of *trans*-diol **5** (184 mg, 89%), a white solid; R_f = 0.25 (50% EtOAc in hexane); $[\alpha]_D$ +35.9 (c 1.0, CHCl₃); HRMS (ES) calcd for C₁₅H₂₀NO₅ (M + NH₄)⁺ 294.1341 found 294.1355; ¹H-NMR (600 MHz, CDCl₃): δ 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, Me), 1.41 (s, Me); $^{13}\text{C-NMR}$ (150 MHz, CDCl_3): δ 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 $\nu_{\text{max}}/\text{cm}^{-1}$ 3498, 2998, 2902, 1967, 1629, 1220.

(3*aR*, 4*S*, 5*R*, 10*cR*)-4,5-bis((4-methoxybenzyl)oxy)-2,2-Dimethyl-3*a*,4,5,10*c*-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 in *vacuo* 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 0.25 (20% EtOAc in hexane); $[\alpha]_D^{+23.6}$ (c 1.2, CHCl_3); HRMS (ES) calcd for $\text{C}_{31}\text{H}_{32}\text{O}_7\text{Na}$ ($\text{M} + \text{Na}$) $^+$ 539.2046 found 539.2048; $^1\text{H-NMR}$ (600 MHz, CDCl_3): δ 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, H-3*a*), 4.13 (dd, $J = 6.9, 5.8$ Hz, H-4), 3.82 (s, Me), 3.80 (s, Me), 1.50 (s, Me), 1.40 (s, 1H); $^{13}\text{C-NMR}$ (150 MHz, CDCl_3): δ 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 $\nu_{\text{max}}/\text{cm}^{-1}$ 2968, 2931, 2844, 1520, 1261, 1107, 871.

(1*R*, 2*R*, 3*S*, 4*R*)-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 0.22 (50% EtOAc in hexane); $[\alpha]_D^{+19.0}$ (c 1.3, CHCl_3); HRMS (ES) calcd for $\text{C}_{28}\text{H}_{28}\text{O}_7\text{Na}$ ($\text{M} + \text{Na}$) $^+$ 499.1733 found 499.1732; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 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, Me), 3.80 (s, Me); $^{13}\text{C-NMR}$ (150 MHz, CDCl_3): δ 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 $\nu_{\text{max}}/\text{cm}^{-1}$ 3996, 2954, 2917, 2849, 1575, 1542, 1249, 1089, 1011.

(2*S*, 3*S*, 4*R*)-2-Hydroxy-3,4-bis((4-methoxybenzyl)oxy)-3,4-dihydrodibenzo[*b,d*]furan-1(2*H*)-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 in *vacuo* 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 0.30 (30% EtOAc in hexane); $[\alpha]_D^{+34.0}$ (c 0.7, CHCl_3); HRMS (ES) calcd for $\text{C}_{28}\text{H}_{26}\text{O}_7\text{Na}$ ($\text{M} + \text{Na}$) $^+$ 497.1576 found 497.1506; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 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, Me), 3.81 (s, Me), 3.80 (d, $J = 2.0$ Hz, 1H); $^{13}\text{C-NMR}$ (150 MHz, CDCl_3): δ 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 $\nu_{\text{max}}/\text{cm}^{-1}$ 3453, 3070, 2927, 2852, 2778, 1771, 1707, 1625, 1515, 1366, 1169, 1014.

(2*S*, 3*R*, 4*R*)-2-Methoxy-3,4-bis((4-methoxybenzyl)oxy)-3,4-dihydrodibenzo[*b,d*]furan-1(2*H*)-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 in *vacuo* 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 0.24 (20% EtOAc in hexane); $[\alpha]_D^{+47.7}$ (c 0.4, CHCl_3); HRMS (ES) calcd for $\text{C}_{29}\text{H}_{32}\text{NO}_7$ ($\text{M} + \text{NH}_4$) $^+$ 506.2179 found 506.2220; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 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, Me), 3.82 (s, Me), 3.77 (3H, s, Me); $^{13}\text{C-NMR}$ (150 MHz, CDCl_3): δ 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 $\nu_{\text{max}}/\text{cm}^{-1}$ 2969, 2882, 1735, 1679, 1280, 1021, 976.

(2*S*, 3*R*, 4*R*)-3,4-Dihydroxy-2-methoxy-3,4-dihydrodibenzo[*b,d*]furan-1(2*H*)-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 obtained was purified by flash column chromatography (50% EtOAc in hexane) to afford ribisin A (2.9 mg, 63%), a pale-yellow solid; R_f 0.20 (60% EtOAc in hexane); $[\alpha]_D^{+16.0}$ (c 0.2, MeOH); HRMS (ES) calcd for $\text{C}_{26}\text{H}_{24}\text{O}_{10}\text{Na}$ ($2\text{M} + \text{Na}$) $^+$ 519.1267 found 519.1259; $^1\text{H-NMR}$ (600 MHz, CDCl_3): δ 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, OMe); $^{13}\text{C-NMR}$ (150 MHz, CDCl_3): δ 91.3, 169.4, 157.6, 127.2, 126.0, 124.3, 122.9, 116.1, 112.8, 87.2, 78.9, 70.4, 60.8.

(3*aR*, 3*bS*, 5*S*, 6*aS*, 11*cR*)-5-(4-methoxyphenyl)-2,2-Dimethyl-3*a*,3*b*,6*a*,11*c*-tetrahydrobenzo[4',5']furo[2',3':5,6]benzo[1,2-*d*:3,4-*d'*]bis([1,3]dioxole) and (3*aR*, 3*bS*, 5*R*, 6*aS*, 11*cR*)-5-(4-methoxyphenyl)-2,2-Dimethyl-3*a*,3*b*,6*a*,11*c*-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 1-(dimethoxymethyl)-4-methoxybenzene (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 **10a** and **10b** (57:43) as a pale-yellow oil (50 mg, 87%); R_f 0.23 (5% EtOAc in hexane); HRMS (ES)

calcd for $C_{23}H_{22}O_6Na$ ($M + Na$)⁺ 417.1314 found 417.1309; Minor diastereoisomer **10b**: ¹H-NMR (400 MHz, $CDCl_3$): δ 7.74 (dm, $J = 6.9$ Hz, 1H), 7.51 (dm, $J = 7.1$ Hz, 8H), 7.40-7.27 (m, 9H, 10H), 7.14 (d, $J = 8.7$ Hz, 2 x PMB-ArH), 6.76 (d, $J = 8.7$ Hz, 2 x PMB-ArH), 6.02 (s, 5H), 5.44 (d, $J = 5.1$ Hz, 11Hc), 5.39 (d, $J = 6.5$ Hz, 6Ha), 5.01 (dd, $J = 6.5$, 2.8 Hz, 3Hb), 4.91 (dd, $J = 5.1$, 2.8 Hz, 3Ha), 3.72 (s, OMe), 1.46 (s, Me), 1.12 (s, Me). Major diastereoisomer **10a**: ¹H-NMR (400 MHz, $CDCl_3$): δ 7.76 (dm, $J = 7.3$ Hz, 11H), 7.54 (dm, $J = 7.7$ Hz, 8H), 7.39 (d, $J = 8.7$ Hz, 2 x PMB-ArH), 7.37-7.27 (m, 9H, 10H), 5.70 (s, 5H), 5.62 (d, $J = 5.8$ Hz, 11Hc), 5.51 (d, $J = 4.9$ Hz, 6Ha), 5.01 (dd, $J = 5.8$, 3.0 Hz, 3Hb), 4.91 (dd, $J = 5.0$, 3.0 Hz, 3Ha), 3.81 (s, OMe), 1.45 (s, Me), 1.09 (s, Me).

(3*aS*,4*S*,5*S*,10*cR*)-5-((4-methoxybenzyl)oxy)-2,2-Dimethyl-3*a*,4,5,10*c*-tetrahydrobenzo[*b*][1,3]dioxolo[4,5-*e*]benzofuran-4-ol (**11**) and (3*aR*,4*R*,5*S*,10*cR*)-4-((4-methoxybenzyl)oxy)-2,2-Dimethyl-3*a*,4,5,10*c*-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 $-15^\circ C$, was 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 *in vacuo* to give a mixture of diastereomers **10a** and **10b**. The mixture of diastereomers was taken up in dry CH_2Cl_2 (10 mL), cooled to $-78^\circ C$ and treated with a solution of DIBAL (1 M, 4.3 mL) in hexane. The mixture was kept stirred (6 h) at $-78^\circ C$, allowed to warm to room temperature, and a saturated aqueous solution of potassium sodium tartrate (2 mL) added to it. 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 0.21 (30% EtOAc in hexane); $[\alpha]_D +8.4$ (c 1.5, $CHCl_3$); HRMS (ES) calcd for $C_{23}H_{28}NO_6$ ($M + NH_4$)⁺ 414.1917 found 414.1928; ¹H-NMR (600 MHz, $CDCl_3$): δ 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, OMe), 2.83 (d, $J = 4.8$ Hz, 1H), 1.50 (s, Me), 1.33 (s, Me); ¹³C-NMR (150 MHz, $CDCl_3$): δ 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.

Homobenzylic ether **12** (27 mg, 16%); R_f 0.20 (30% EtOAc in hexane); $[\alpha]_D -8.2$ (c 0.9, $CHCl_3$); HRMS (ES) calcd for $C_{23}H_{28}NO_6$ ($M + NH_4$)⁺ 414.1917 found 414.1928; ¹H-NMR (600 MHz, $CDCl_3$): δ 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, OMe), 2.64 (d, $J = 7.5$ Hz, 1H), 1.51 (s, Me), 1.43 (s, Me); ¹³C-NMR (150 MHz, $CDCl_3$): δ 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**.

(3*aR*,4*S*,5*S*,10*cR*)-4-Methoxy-5-((4-methoxybenzyl)oxy)-2,2-dimethyl-3*a*,4,5,10*c*-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 μ L). The reaction mixture was stirred (4 h) at room temperature, the solvent removed *in vacuo*, 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 0.24 (20% EtOAc in hexane); $[\alpha]_D -95.6$ (c 0.5, $CHCl_3$); HRMS (ES) calcd for $C_{24}H_{30}NO_6$ ($M + NH_4$)⁺ 428.2073 found 428.2052; ¹H-NMR (600 MHz, $CDCl_3$): δ 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, $J = 7.61$ 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, OMe), 3.67 (dd, $J = 8.5$, 3.6 Hz, 1H), 3.48 (s, OMe), 1.52 (s, Me), 1.49 (s, Me); ¹³C-NMR (150 MHz, $CDCl_3$): δ 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.

(1*R*,2*R*,3*S*,4*S*)-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-H₂O (9:1, 2 mL) was treated with TFA (10 μ L). The reaction mixture was stirred (50°C) overnight, concentrated *in vacuo*, 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 0.25 (60% EtOAc-hexane); $[\alpha]_D -139.0$ (c 0.7, $CHCl_3$); HRMS (ES) calcd for $C_{21}H_{22}O_6Na$ ($M + Na$)⁺ 393.1314 found 393.1302; ¹H-NMR (600 MHz, $CDCl_3$): δ 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, OMe), 3.78 (dd, $J = 10.1$, 3.9 Hz, 1H), 3.39 (s, OMe), 3.22 (br s, 2H); ¹³C-NMR (150 MHz, $CDCl_3$): δ 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.

(2*S*,3*S*,4*S*)-2-Hydroxy-3-methoxy-4-((4-methoxybenzyl)oxy)-3,4-dihydrodibenzo[*b,d*]furan-1(2*H*)-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, the volatiles were removed *in vacuo*, 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 0.33 (50% EtOAc in hexane); $[\alpha]_D -118.0$ (c 1.0, $CHCl_3$); HRMS (ES) calcd for $C_{21}H_{20}O_6Na$ ($M + Na$)⁺ 391.1158 found 391.1155; ¹H-NMR (600 MHz, $CDCl_3$): δ 8.08 (dm, 1H), 7.58 (m, 1H), 7.44 (td, $J = 7.3$, 1.5 Hz, 1H), 7.42-7.38 (m, 8H, 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, OMe), 3.72 (dd, $J = 9.9$, 3.7 Hz, 1H), 3.59 (d, $J = 1.2$ Hz, 1H), 3.54 (3H, s, OMe); ¹³C-NMR (150 MHz,

CDCl₃): δ 191.5, 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 $\nu_{\text{max}}/\text{cm}^{-1}$ 3844, 3681, 2948, 2880, 1652, 1410, 1128, 1044, 852.

(2*S*,3*R*,4*S*)-2,3-Dimethoxy-4-((4-methoxybenzyl)oxy)-3,4-dihydrodibenzo[*b,d*]furan-1(2*H*)-one (**16**). Following the procedure described for the synthesis of methyl ether **9**, a mixture of ketone **15** (9.2 mg, 0.025 mmol), Ag₂O (8.0 mg) and MeI (10 μ L) 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 = 0.21 (30% EtOAc in hexane); $[\alpha]_D$ -139.0 (c 0.7, CHCl₃); HRMS (ES) calcd for C₂₂H₂₃O₆ ($M + H$)⁺ 383.1495 found 383.1471; ¹H-NMR (600 MHz, CDCl₃): δ 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, OMe), 3.70 (s, OMe), 3.52 (s, OMe); ¹³C-NMR (150 MHz, CDCl₃): δ 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 $\nu_{\text{max}}/\text{cm}^{-1}$ 2947, 2880, 1739, 1684, 1484, 1281, 1041.

(2*S*,3*R*,4*S*)-4-hydroxy-2,3-dimethoxy-3,4-dihydrodibenzo[*b,d*]furan-1(2*H*)-one (Ribisin B). ^{1,7}

Following the procedure described for the last step in the synthesis of ribisin A, a solution of dimethoxy ketone **16** (7.6 mg, 0.020 mmol) in CH₂Cl₂ and H₂O (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%), a colorless oil; R_f = 0.25 (30% EtOAc in hexane); $[\alpha]_D$ -25.8 (c 0.4, CHCl₃); HRMS (ES) calcd for C₁₄H₁₅O₅ ($M + H$)⁺ 263.0919 found 263.0912; ¹H-NMR (600 MHz, CDCl₃): δ 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, OMe), 3.61 (s, OMe), 3.05 (d, J = 7.1 Hz, 1H); ¹³C-NMR (150 MHz, CDCl₃): δ 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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