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Chemoenzymatic Total Syntheses of Ribisins A, B, and D, Polyoxygenated Benzofuran Derivatives Displaying NGF-Potentiating Properties

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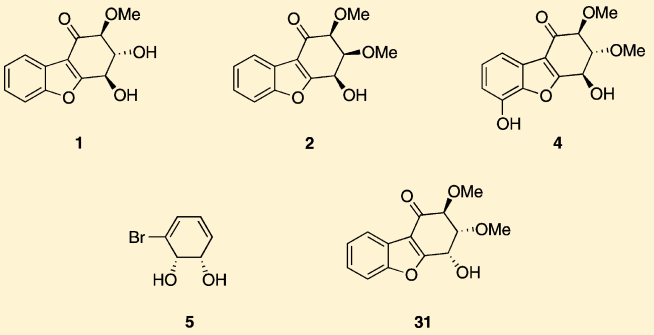
Supporting Information

ABSTRACT: Total syntheses of the structures, **1**, **2**, and **4**, assigned to the biologically active natural products ribisins A, B, and D, respectively, have been achieved using the microbially derived and enantiomerically pure *cis*-1,2-dihydrocatechol **5** as starting material. Key steps include Suzuki–Miyaura cross-coupling, intramolecular Mitsunobu, and tandem epoxidation/rearrangement reactions. As a result of these studies, the structures of ribisins A and D have been confirmed while that of congener B was shown to be represented by **31** rather than **2**.

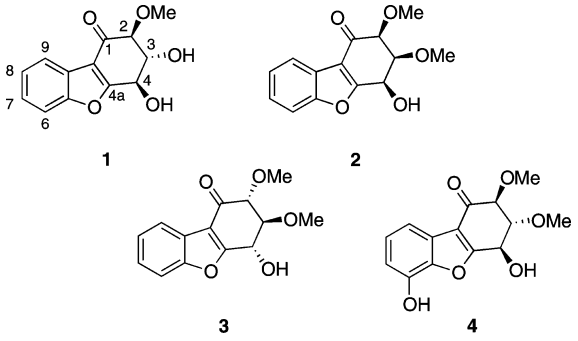


INTRODUCTION

In late 2012, Fukuyama and co-workers reported[1] the outcomes of an investigation of the active principals associated with *Phellinus ribis* (Schmach.) Quél (Hymenochaetaceae), a white-rot fungus found in several East Asian countries and the fruiting bodies of which have been exploited in traditional medicines for promoting immunity and for the treatment of gastrointestinal cancer.[2] In particular, they described the isolation (in milligram amounts) and structural assignment of four novel polyoxygenated benzofuran derivatives, namely ribisin A (**1**), ribisin B (**2**), ribisin C (**3**), and ribisin D (**4**). Their structures, including relative stereochemistries, were proposed on the basis of various spectroscopic analyses, particularly those involving ^{1}H and ^{13}C NMR studies, while the illustrated absolute configurations followed from the application of CD exciton chirality methods to the readily derived *p*-bromobenzoates.

Ribisins A − D were shown[1] to enhance neurite outgrowth in nerve growth factor (NGF)-mediated PC12 cells in a dose-dependent way and in the micromole range with ribisin C being the most active member of the series. The variation in activity of these compounds as a function of changes in both stereochemistry and substituent suggests that they could represent novel leads for creating drugs that reduce neuronal damage as a result of stroke and other trauma and might even have application in the development of new therapeutic agents for the treatment of Alzheimer's disease.[1]

As a result of their novel structures and interesting biological properties, we embarked on a program to develop syntheses of the ribisins so as to generate material for extended biological evaluation. The outcomes of our initial studies in the area,[3] which culminated in a 10-step synthesis of compound **3** from the microbially derived and enantiomerically pure *cis*-1,2-dihydrocatechol **5**,[4] revealed that the absolute stereochemistry



of ribisin C had been incorrectly assigned and is, in fact, represented by structure *ent*-**3**. As a consequence, we also developed[3] a 14-step total synthesis of compound *ent*-**3** from the same starting material, viz. *cis*-1,2-dihydrocatechol **5**, and thereby clearly established the true structure of ribisin C. Of course, this sequence also provided biologically active material for further testing. These preliminary results prompted us to pursue total syntheses of the remaining members of the ribisin family, namely congeners A, B, and D in order to either confirm their structures or establish the correct ones. Herein we detail the outcome of these studies that, inter alia, provide the means for obtaining all of the ribisins in quantities suitable for comprehensive biological evaluation.

RESULTS AND DISCUSSION

The key features of our recently reported[3] total synthesis of ribisin C (*ent*-**3**) were a Suzuki–Miyaura cross-coupling

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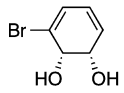
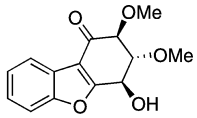


5



ent-3

reaction between a dimethoxy-substituted derivative of compound **5** and the commercially available 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol. This was followed by the immediate engagement of the product of this process in an intramolecular Mitsunobu reaction with the pendant phenolic hydroxyl group serving as an internal nucleophile. The resulting 2,3,4,4a-tetrahydrodibenzo[*b*,*d*]furan was treated with *m*-chloroperbenzoic acid (*m*-CPBA), and the epoxide thus formed underwent a spontaneous isomerization to give the corresponding allylic alcohol now incorporating a fully aromatic benzofuran substructure. Oxidation of the associated hydroxyl then allowed for introduction of the necessary C1-carbonyl moiety (see structure **1** for atom numbering). Another important feature of our earlier work[3] was the use of an α-chloroacetate group to protect the C4-hydroxyl group since this can be cleaved under exceptionally mild conditions so as to reveal the seemingly rather fragile polyoxygenated cyclohexenone-type substructure associated with the final target.[5] Attempts to cleave the corresponding acetate using potassium carbonate in methanol only resulted in a complex mixture of products.

Given the structural similarities between the various ribisin structures, the above-mentioned synthetic protocols would seem suitable for deployment in syntheses of the targeted members of the family, namely compounds **1**, **2**, and **4**. In many respects, then, a major focus of the present work was the manipulation of the nonhalogenated double bond within the starting diene **5** in ways that allowed for the introduction of the relevant functionalities at C2 and C3 in the title compounds. Details of the successful implementation of these protocols are provided in the following sections.

Total Synthesis of Ribisin A. The reaction sequence leading to the preparation of ribisin A (**1**) is presented in Scheme 1. Thus, a dichloromethane solution of the starting diol **5** maintained at 0 °C was treated with *p*-methoxybenzaldehyde dimethyl acetal (*p*-MBDMA) in the presence of (+)-camphorsulfonic acid (CSA), and the previously reported[6] *p*-methoxyphenyl (PMP) acetal **6** was thereby obtained as a single diastereoisomer. Immediate subjection of the latter compound to reaction with diisobutylaluminum hydride (DIBAl-H) resulted in regioselective cleavage of the acetal moiety and formation of the known[6,7] *p*-methoxybenzyl (PMB) ether **7**, which was obtained in 74% yield over the two steps involved. Treatment of compound **7** with *N*-bromosuccinimide (NBS) in wet THF resulted in the selective formation of the previously unreported bromohydrin **8** (76%) that was immediately treated with sodium methoxide in methanol. It is presumed that the initial product of reaction is the epoxide **9**, but this reacts, in situ, to give, via nucleophilic ring-opening at

Scheme 1. Total Synthesis of Ribisin A (1)

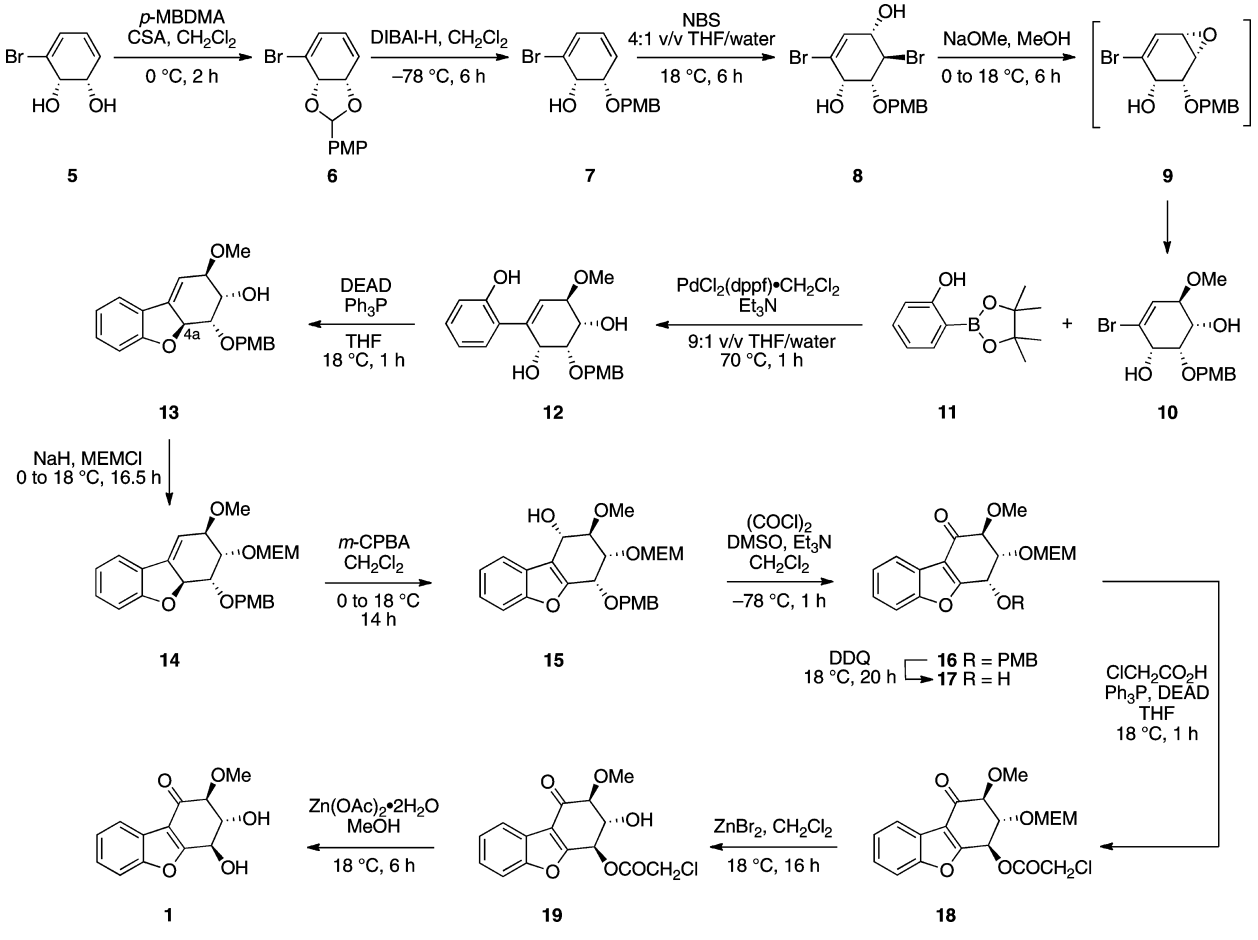


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Table 1. Comparison of the ^{13}C and ^{1}H NMR Data Recorded for Synthetically Derived Compound 1 with Those Reported for Ribisin A

^{13}C NMR (δ_C)		^{1}H NMR (δ_H)	
compd 1[a]	ribisin A[b]	compd 1[c]	ribisin A[d]
193.1	193.1	7.99 (broad dd, J = 7.5 and 1.2 Hz, 1H)	7.97 (ddd, J = 7.5, 1.4, and 0.7 Hz, 1H)
169.3	169.2	7.61 (broad d, J = 7.5 Hz, 1H)	7.52 (ddd, J = 7.5, 1.0, and 0.7 Hz, 1H)
157.4	157.4	7.46−7.35 (complex m, 2H)	7.40 (td, J = 7.4 and 1.4 Hz, 1H)
127.1	127.1		7.36 (td, J = 7.5 and 1.0 Hz, 1H)
125.9	125.9	5.00 (d, J = 7.3 Hz, 1H)	4.97 (d, J = 7.5 Hz, 1H)
124.3	124.3	4.04 (d, J = 9.8 Hz, 1H)	4.01 (d, J = 9.8 Hz, 1H)
122.8	122.8	4.00 (dd, J = 9.8 and 7.3 Hz, 1H)	3.97 (dd, J = 9.8 and 7.5 Hz, 1H)
116.1	116.1	3.74 (s, 3H)	3.71 (s, 3H)
112.7	112.7	signals due to OH protons not observed	
87.1	87.1		
78.8	78.8		
70.3	70.3		
60.8	60.8		

[a]Recorded in CD_3OD at 100 MHz. [b]Obtained from ref 1 and recorded in CD_3OD at 150 MHz. [c]Recorded in CD_3OD at 400 MHz. [d]Obtained from ref 1 and recorded in CD_3OD at 600 MHz.

the allylic carbon, the diol **10** in 82% yield and as the only isolable product. Suzuki−Miyaura cross-coupling of this last compound with 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (**11**)[8] using $PdCl_2(dppf)\cdot CH_2Cl_2$ as the source of catalyst and triethylamine as base afforded the anticipated product **12** in 80% yield. Interestingly, and in contrast to our experience[3] when carrying out the analogous cross-coupling reaction en route to compound **3**, no biaryl(s) arising from elimination of the elements of methanol and water within the primary coupling product was (were) observed in this instance. Treatment of compound **12** with diethyl azodicarboxylate (DEAD) in the presence of triphenylphosphine resulted in an intramolecular Mitsunobu reaction with the phenolic OH group serving as the internal nucleophile, thus affording the benzofuran isomer **13** in 88% yield and so establishing the tricyclic framework of target **1**. The illustrated β-configuration at C4a (ribisin numbering) within this product, which is of no consequence in terms of the overall synthesis, was assigned on the basis of the well-known propensity of the Mitsunobu reaction to proceed with inversion of configuration at the center undergoing substitution.[9] The alcohol **13** was protected as the corresponding β-methoxyethoxymethyl (MEM) ether **14** (80%) under standard conditions and the latter compound subjected to reaction with *m*-CPBA. This resulted in the formation of the benzofuran **15**, presumably through spontaneous rearrangement of the initially formed epoxide (a process driven by cleavage of the strained three-membered ring and accompanying formation of an aromatic ring system). The illustrated α-orientation of the C1-hydroxy group within compound **15**, a rather unstable material, is tentatively assigned on the basis that the initial epoxidation reaction will proceed from that face of the alkene opposite to the allylically positioned and β-configured methoxy group. Oxidation of alcohol **15** under Swern conditions afforded compound **16** (70% from **14**), the PMB group of which was cleaved using DDQ to afford the γ-hydroxy ketone **17** in 81% yield. The last compound was engaged in an intermolecular Mitsunobu reaction using α-chloroacetic acid as the nucleophile and thus affording the ester **18** in 85% yield. The MEM ether residue within compound **18** was cleaved using zinc(II) bromide in dichloromethane[10] and the product diol monoester **19** treated with zinc acetate dihydrate in methanol,[11] thereby affording the target compound **1** in 50% yield over the two steps.

All the spectroscopic data acquired on compound **1** were in complete accord with the assigned structure but final confirmation of this followed from a single-crystal X-ray analysis, details of which are provided in the Experimental Section and Supporting Information. Furthermore, the ^{13}C and ^{1}H NMR spectral data recorded for this material compared favorably (see Table 1) with those reported[1] by Fukuyama and co-workers for ribisin A.

Since the specific rotations were also a good match {$[\alpha]^{20}_D$ −24.9 (*c* 1.2, methanol) for synthetically derived **1** vs $[\alpha]^{25}_D$ −21.9 (*c* 1.0, methanol) reported for ribisin A}, we conclude that the structure of this natural product has been correctly assigned. This outcome agrees with that of Du and co-workers who have very recently completed a synthesis of the same compound starting from methyl α-D-glucopyranoside.[12]

Total Synthesis of the Structure Assigned to Ribisin B. The next structure targeted for synthesis was that assigned to ribisin B, namely the *all-cis* and dimethoxylated system **2**. In the early stages of the synthetic sequence (Scheme 2), the well-known acetonide derivative (**20**)[13] of the starting diol **5** was subjected to a completely facially selective *cis*-dihydroxylation of the nonhalogenated double bond under Upjohn conditions,[14] thereby affording the previously reported[13,15] diol **21** in 75% yield (from **5**). Two-fold *O*-methylation of the last compound was achieved using methyl iodide in the presence of sodium hydride, and the bis-ether **22** (98%) thus obtained subjected to treatment with aqueous acetic acid at 70 °C for 14 h. A dichloromethane solution of the diol **23** so-formed (97%) was exposed to *p*-MBDMA in the presence catalytic quantities of *p*-TsOH and the ensuing PMP-acetal immediately subjected to reductive cleavage using DIBAl-H and thereby delivering the alcohol **24** (50% from **23**). Suzuki−Miyaura cross-coupling of the last compound with arylboronate ester **11** then afforded the expected product **25** (81%) that could be engaged in an intramolecular Mitsunobu reaction to give the tricyclic compound **26** in 89% yield. Reaction of alkene **26** with *m*-CPBA gave, via in situ rearrangement of the initially formed epoxide, benzofuran **27** that, because of its instability, was immediately oxidized under Swern conditions to afford the enone **28** (61% from **26**), the PMB ether residue of which was

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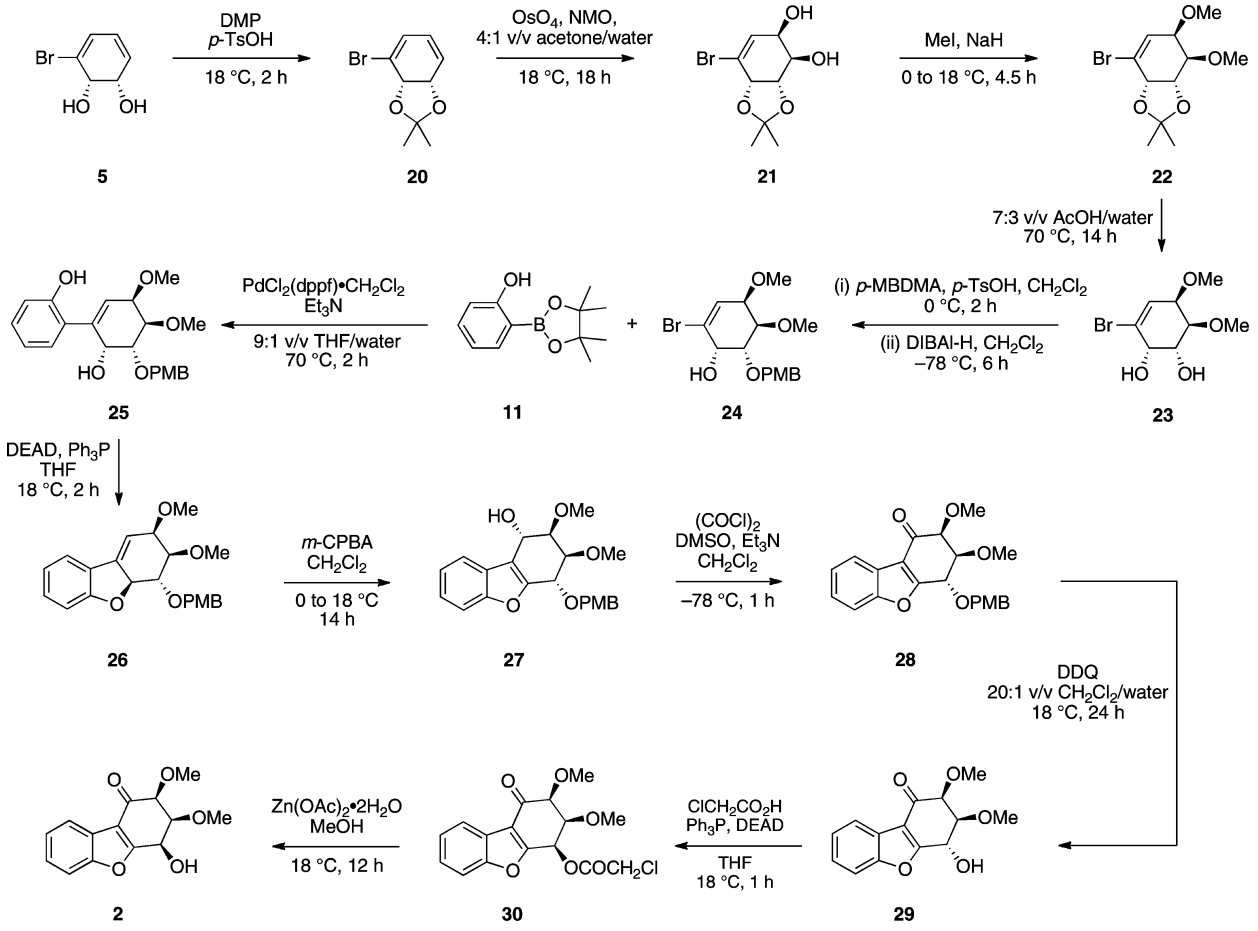
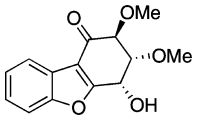
Scheme 2. Total Synthesis of Compound 2, the Structure Incorrectly Assigned to Ribisin B



cleaved with DDQ to afford alcohol **29** (85%). Subjection of the last compound to an intermolecular Mitsunobu reaction using α-chloroacetic acid as the nucleophile then gave the *all-cis*-configured ester **30** (71%) that on methanolysis in the presence of the dihydrate of zinc acetate afforded the targeted structure **2** in 82% yield.

All of the spectral data acquired on compound **2** were in accord with the assigned structure, but final confirmation of this followed from a single-crystal X-ray analysis. Details are provided in the Experimental Section and Supporting Information. However, in contrast to the case of ribisin A (as detailed above), the spectral data acquired on compound **2** did not match those reported for the natural product ribisin B. Thus, the ^{13}C and ^{1}H NMR spectral data (see the Supporting Information) were quite different. The same was true for the specific rotations $\{[\alpha]^{20}_{D}$ +51.9 (*c* 0.4, methanol) for synthetically derived **2** vs $[\alpha]^{25}_{D}$ −91.1 (*c* 0.4, methanol) reported[1] for ribisin B$\}$. These results clearly suggest that ribisin B is a diastereoisomer or, perhaps (even), a structural isomer of compound **2**. The fortuitous identification of the true structure of this natural product is described in the following section.

Identification of the True Structure of Ribisin B. While examining the ^{13}C NMR spectral data obtained on the various intermediates generated during the course of our synthesis of the true structure, *ent*-**3**, of ribisin C we noted that those due to its C4-epimer, viz. compound **31**, displayed essentially identical chemical shifts to those reported[1] for ribisin B. On the basis of further comparisons of the relevant sets of spectral data, details of which are presented below, we have concluded that the true structure of ribisin B is represented by **31** and not by **2**.



31

For the sake of completeness, the synthetic route employed in our earlier studies[3] for the purpose of obtaining compound **31** (and, thereby, ribisin C) is reproduced in Scheme 3. Thus, the starting diol **5** was reacted with NBS in wet THF and so forming, in a regio- and diastereo-selective process, a bromohydrin that was immediately converted into the acetonide **32** (73%) under standard conditions. Treatment of the latter material with sodium methoxide in methanol then lead, in a manner analogous to that involved in the sequence **8** → **9** → **10** (Scheme 1), to compound **33** (90%). Manipulation of alcohol **33** in a similar fashion to that associated with the early stages of the synthesis of compound **2** (Scheme 2) lead, via compounds **34** (97%) and **35** (93%), to the conduritol **36** (57%). This last compound was then engaged in a Suzuki–Miyaura cross-coupling reaction with boronate ester **11** to give the arylated cyclohexene **37** (83%). Subjection of compound **37** to the now familiar sequence involving an intramolecular Mitsunobu reaction (leading to tricycle **38** in 89% yield), epoxidation/rearrangement then Swern oxidation (delivering

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Scheme 3. Total Synthesis of Compound 31, the True Structure of Ribisin B

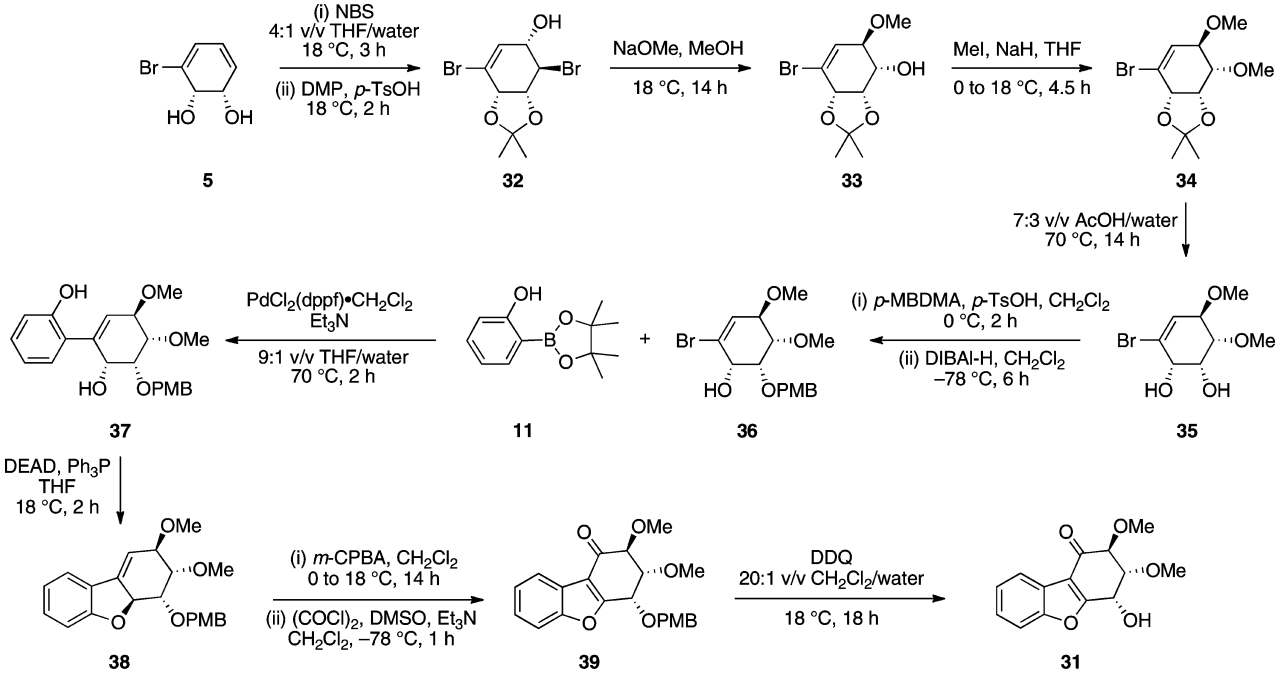


Table 2. Comparison of the ^{13}C and ^{1}H NMR Data Recorded for Synthetically Derived Compound 31 with Those Reported for Ribisin B

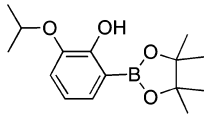
^{13}C NMR (δ_C)		^{1}H NMR (δ_H)	
compd **31**[a]	ribisin B[b]	compd **31**[c]	ribisin B[d]
190.2	190.2	8.05 (dm, *J* = 7.5 Hz, 1H)	8.07 (ddd, *J* = 7.4, 1.6, and 0.6 Hz, 1H)
165.2	165.2	7.53 (dm, *J* = 7.5 Hz, 1H)	7.55 (ddd, *J* = 7.4, 1.3, and 0.6 Hz, 1H)
155.7	155.8	7.39−7.32 (complex m, 2H)	7.39 (td, *J* = 7.4 and 1.6 Hz, 1H)
126.0	126.1		7.37 (td, *J* = 7.4 and 1.3 Hz, 1H)
124.8	124.9	5.29 (dd, *J* = 6.9 and 4.0 Hz, 1H)	5.30 (dd, *J* = 7.0 and 4.1 Hz, 1H)
123.0	123.0	4.14 (d, *J* = 7.5 Hz, 1H)	4.16 (d, *J* = 6.6 Hz, 1H)
122.2	122.3	3.98 (dd, *J* = 6.9 and 4.0 Hz, 1H)	4.00 (dd, *J* = 6.6 and 4.1 Hz, 1H)
115.2	115.3	3.60 (s, 3H)	3.62 (s, 3H)
111.7	111.8	3.60 (s, 3H)	3.62 (s, 3H)
81.8	81.8	3.17 (d, *J* = 6.9 Hz, 1H)	3.05 (d, *J* = 7.0 Hz, 1H)
81.6	81.6		
63.7	63.7		
59.7	59.7		
59.4	59.4		

[a]Recorded in CD_3OD at 100 MHz. [b]Obtained from ref 1 and recorded in CD_3OD at 150 MHz. [c]Recorded in CD_3OD at 400 MHz. [d]Obtained from ref 1 and recorded in CD_3OD at 600 MHz.

compound **39** in 48% yield) and then cleavage of the PMB ether (once again using DDQ) afforded compound **31** (85%).

Comparisons of the ^{13}C and ^{1}H NMR spectral data recorded on compound **31** with those reported for ribisin B are presented in Table 2 and reveal good matches and thus suggesting they are one and the same compound. Disappointingly, and despite strenuous efforts, we have been unable to grow crystals of compound **31** suitable for X-ray analysis. The specific rotation of the synthetically derived material was of the same sign but considerably larger magnitude than that reported for the natural product {$[\alpha]^{20}_D$ −168.5 (*c* 0.6, methanol) vs $[\alpha]^{25}_D$ −91.1 (*c* 0.4, methanol) reported[1] for ribisin B}, and this discrepancy is attributed to the presence of impurities in the latter which was only isolated in 1.6 mg quantities (more than 200 mg of synthetic material was obtained).

Total Synthesis of Ribisin D. In order develop a synthesis of the structure, **4**, proposed by Fukuyama and co-workers for the natural product ribisin D a new boronate ester building block was required. The one identified as being most appropriate for this purpose was compound **40** because of the prospects of being able to cleave aryl isopropyl ethers under mild conditions[16] and thus revealing a phenolic hydroxyl group as required at C6 in target **4**.



40

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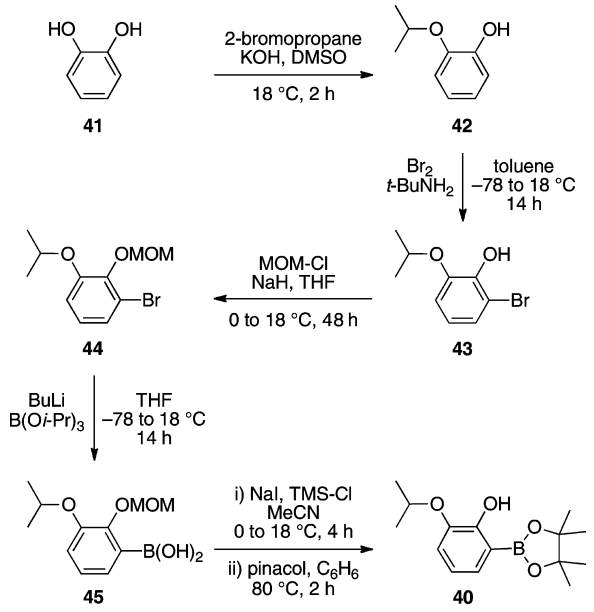
The reaction sequence employed in preparing aryl boronate **40** is shown in Scheme 4 and involved initial monoisopropylation of catechol **41** under conditions described by Waldmann and co-workers and thus affording phenol **42**[17] (45%). Electrophilic aromatic bromination of the latter compound using molecular bromine in the presence of *tert*-butylamine afforded the 1,2,3-trisubstituted arene **43**[17] (81%), and this was immediately protected, under conventional conditions, as the corresponding and previously unreported methoxymethyl (MOM) ether **44** (96%). Treatment of compound **44** with *n*-BuLi in THF at −78 °C and trapping of the resulting lithiated arene with triisopropyl borate gave, after warming of the reaction mixture to 18 °C and quenching it with water, the anticipated boronic acid **45**. After removing the associated MOM protecting group using NaI/TMSCl in acetonitrile, the last compound was immediately treated with pinacol in refluxing benzene in an apparatus fitted with a Dean−Stark trap, thus providing, after conventional workup, the boronate ester **40** (45% from **44**). All the spectroscopic data acquired on ester **40** were in complete accord with the assigned structure.

With building block **40** to hand its exploitation in the synthesis of compound **4** could be pursued. The ultimately successful reaction sequence used for this purpose is shown in Scheme 5 and involved initial Suzuki−Miyaura cross-coupling of compounds **36** and **40**, thereby generating the arylated cyclohexene **46** in 92% yield. This last compound readily participated, under the usual reaction conditions, in an intramolecular Mitsunobu reaction to deliver the cyclodehydration product **47** (94%), and this was subjected to an epoxidation/rearrangement sequence and so delivering an allylic alcohol that was immediately oxidized under Swern conditions to give the ketone **48** (58% over two steps). Cleavage of the associated PMB ether moiety within the last compound was achieved using DDQ and the resulting free alcohol **49** (84%) subjected to an intermolecular Mitsunobu reaction using α-chloroacetic acid, thus providing ester **50** in 84% yield. Methanolysis of this ester under the usual conditions then gave compound **51**, the isopropyl ether of target compound **4**. The cleavage of the aryl isopropyl ether

Scheme 4. Synthesis of Boronate Ester 40



Scheme 5. Total Synthesis of Ribisin D (4)

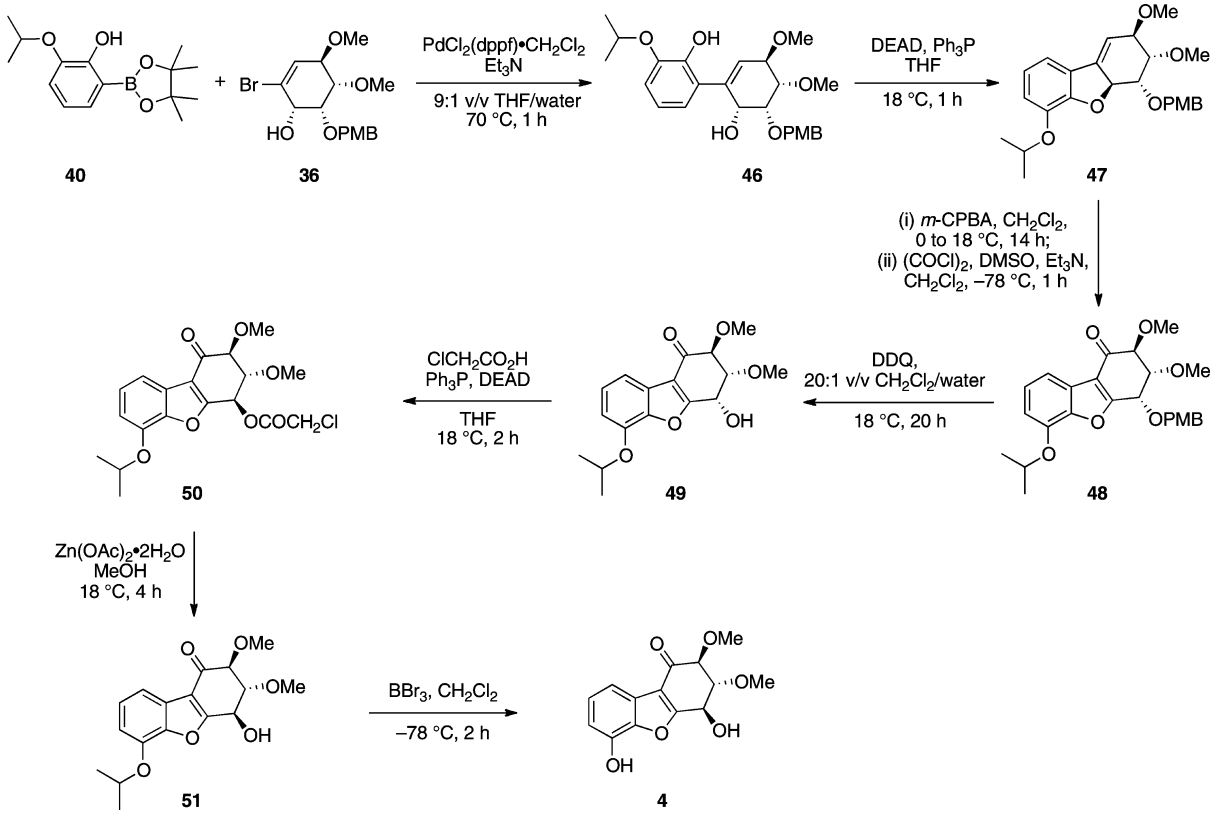


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Table 3. Comparison of the ^{13}C and ^{1}H NMR Data Recorded for Synthetically Derived Compound 4 with Those Reported for Ribisin D

^{13}C NMR (δ_C)		^{1}H NMR (δ_H)	
compd 4[a]	ribisin D[b]	compd 4[c]	ribisin D[d]
192.8	192.8	7.39 (dd, J = 7.7 and 1.0 Hz, 1H)	7.41 (dd, J = 7.7 and 1.0 Hz, 1H)
168.7	168.7	7.24 (t, J = 7.7 Hz, 1H)	7.16 (t, J = 7.7 Hz, 1H)
146.2	**146.4**	6.83 (dd, J = 7.7 and 1.0 Hz, 1H)	6.83 (dd, J = 7.7 and 1.0 Hz, 1H)
144.1	**144.5**	5.04 (d, J = 7.5 Hz, 1H)	5.06 (d, J = 7.6 Hz, 1H)
126.8	126.9	4.08 (d, J = 9.7 Hz, 1H)	4.11 (d, J = 9.8 Hz, 1H)
126.0	125.9[e]	3.69 (s, 3H)	3.71 (s, 3H)
116.4	116.4	3.69 (s, 3H)	3.71 (s, 3H)
113.6	113.7	3.67 (dd, J = 9.7 and 7.5 Hz, 1H)	3.69 (dd, J = 9.8 and 7.6 Hz, 1H)
113.4	**113.0**	signals due to hydroxyl group not observed	
88.7	88.8		
86.9	87.0		
69.8	69.9		
61.5	61.5		
61.0	61.0		

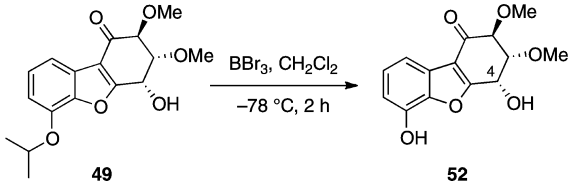
[a]Recorded in CD_3OD at 100 MHz. [b]Obtained from ref 1 and recorded in CD_3OD at 150 MHz. [c]Recorded in CD_3OD at 400 MHz. [d]Obtained from ref 1 and recorded in CD_3OD at 600 MHz. [e]Calculated from inspection of the ^{13}C NMR spectrum shown in the Supporting Information associated with ref 1; we believe the tabulated value of δ_C for C9a of 125.4 in ref 1 is an error.

associated with the former compound proved challenging. So, for example, exposure of it to $AlCl_3$ in dichloromethane at 18 °C had no effect while the use of the more reactive BCl_3 under essentially the same conditions resulted in the formation of various and thus far incompletely characterized but evidently fully aromatic products. Eventually it was established that reaction of substrate **51** with BBr_3 in dichloromethane at −78 °C for 2 h resulted in its partial conversion into target **4** (36% from **50**). Attempts to "push" this conversion to completion only resulted in the rapid formation of fully aromatic products as observed earlier.

Despite the difficulties associated with carrying out the final step of the above-mentioned reaction sequence, sufficient quantities of compound **4** could be accumulated so as to allow for its complete spectroscopic characterization. All of the data thus acquired were in complete accord with the assigned structure and final confirmation of this followed from a single-crystal X-ray analysis, details of which are presented in the Experimental Section and the Supporting Information. A comparison (Table 3) of the ^{13}C and ^{1}H NMR spectral data acquired on compound **4** with those reported[1,18] for ribisin D reveals a good but not a perfect match. In particular, the signals due to the aromatic carbons C5, C6, and C9 (see bolded values in Table 3, assignments due to Fukuyama et al.[1]) had $\Delta\delta_C$ values of >0.1 ppm (146.2 vs 146.4, 144.1 vs 144.5 and 113.4 vs 113.0, respectively). As a result of carrying out a range of relevant experiments (see Table S3 in the Supporting Information), we attribute these differences to variations in pH between the samples rather than, for example, to variations in concentration. As was the case earlier, the specific rotation of the synthetically derived material was of the same sign but considerably larger magnitude than that reported for the natural product {$[\alpha]^{20}_D$ −39.3 (*c* 0.8, methanol) vs $[\alpha]^{24}_D$ −22 (*c* 0.2, methanol) reported[1] for ribisin D}. Once again, this discrepancy is attributed to the presence of impurities in the latter which was only isolated in 1.4 mg quantities (more than 40 mg of synthetic material was obtained).

Synthesis of C4-*epi*-Ribisin D. Given the minor discrepancies in ^{13}C NMR chemical shifts mentioned immediately above and highlighted in Table 3, we sought to explore how much variation in spectroscopic properties might be observed as a result of changing the stereochemistry in compound **4**. Accordingly, we deliberately sought to generate its C4-epimer. This was readily achieved (Scheme 6) by cleaving the isopropyl ether residue associated with compound **49** (an intermediate en route to ribisin D) using BBr_3 in dichloromethane at −78 °C. By such means the desired compound, **52**, was obtained in 57% yield. The spectroscopic data for the synthetic material were entirely consistent with assigned structure C4-*epi*-ribisin D (**52**), and distinct from the data for ribisin D. A comparison (see Supporting Information) of the derived ^{13}C and ^{1}H NMR data with those reported for ribisin D reveal, for example, $\Delta\delta_C$ values of up to 5.9 ppm, thus leaving no doubt that these are different compounds.

Scheme 6. Synthesis of C4-*epi*-Ribisin D (52)



CONCLUSION

The work detailed above, when considered in conjunction with our earlier studies,[3] has clearly established that ribisins A−D are represented by **1**, **31**, *ent*-**3**, and **4**, respectively. Accordingly, in all instances these natural products possess the 2*S*,3*R* configurations with variations only being observed in the degree of *O*-methylation, the extent of oxygenation on the aromatic ring and/or the stereochemistry at C4.

The synthetic protocols used to obtain the title natural products and certain analogues seem to be robust ones that should provide the capacity to generate a significant number of variants if that becomes a worthwhile pursuit. Our current efforts are focused on undertaking a comprehensive biological evaluation of the various compounds we have produced to date. Results will be reported in due course.

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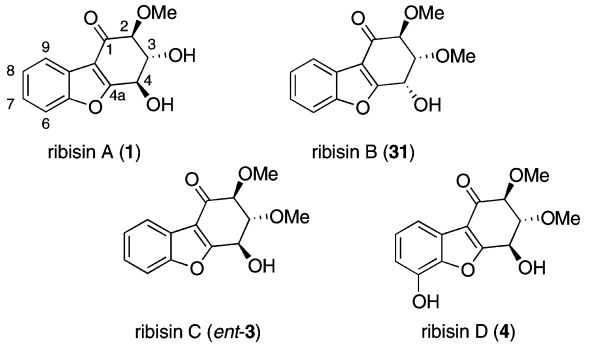

EXPERIMENTAL SECTION

General Experimental Procedures. Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at room temperature in either base-filtered $CDCl_3$ or in CD_3OD on a spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) J (Hz), relative integral] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. The signal due to residual $CHCl_3$ and CD_3OD appearing at δ_H 7.26 and 3.30, respectively, and the central resonance of the $CDCl_3$ "triplet" appearing at δ_C 77.0 or that of the CD_3OD "multiplet" centered at δ_C 49.0 were used to reference ^{1}H and ^{13}C NMR spectra, respectively. Samples were analyzed by infrared spectroscopy (ν_{max}) as thin films on KBr plates. Low-resolution ESI mass spectra were recorded on a single quadrupole liquid chromatograph−mass spectrometer, while high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on a magnetic-sector machine. Melting points are uncorrected. Analytical thin-layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid: ceric sulfate: sulfuric acid (conc.): water (37.5 g: 7.5 g: 37.5 g: 720 mL) or potassium permanganate: potassium carbonate: 5% sodium hydroxide aqueous solution: water (3 g: 20 g: 5 mL: 300 mL). Flash chromatographic separations were carried out following protocols defined by Still et al.[19] with silica gel 60 (40−63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials, reagents, drying agents and other inorganic salts were generally commercially available and were used as supplied. Tetrahydrofuran (THF), methanol and dichloromethane were dried using a solvent purification system that is based upon a technology originally described by Grubbs et al.[20] Where necessary, reactions were performed under a nitrogen atmosphere.

Compound 8. A magnetically stirred mixture of alcohol **7**[6,7] (1.20 g, 3.86 mmol) in THF/water (20 mL of a 4:1 v/v mixture) maintained at 0 °C was treated, in small portions, with NBS (690 mg, 3.88 mmol) over 0.17 h. The resulting solution was warmed to 18 °C over 6 h and then diluted with $Na_2S_2O_3$ (20 mL of a saturated aqueous solution). The mixture thus obtained was extracted with ethyl acetate (2 × 40 mL), and the combined organic phases were washed with brine (1 × 50 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting light yellow oil was subjected to flash chromatography (silica, 1:3 v/v ethyl acetate/hexane elution) to afford, after concentration of the relevant fractions (R_f = 0.2), bromohydrin **8** (1.20 g, 76%) as an amorphous, white powder: $[\alpha]^{20}_D$ −44.0 (c 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 8.7 Hz, 2H), 6.91 (d, J = 8.7 Hz, 2H), 6.27 (d, J = 3.6 Hz, 1H), 4.75 (d, J = 10.9 Hz, 1H), 4.63 (d, J = 10.9 Hz, 1H), 4.42 (dd, J = 6.0 and 4.2 Hz, 1H), 4.28−4.26 (complex m, 2H), 3.87−3.84 (complex m, 1H), 3.82 (s, 3H), 2.72 (d, J = 6.0 Hz, 1H), 2.66 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 131.5, 130.1, 128.4, 125.3, 114.2, 77.9, 73.6, 72.6, 69.7, 55.3, 50.8; IR ν_{max} 3393, 2904, 1611, 1513, 1463, 1303, 1248, 1175, 1106, 1035, 871, 820, 743 cm^{-1}; MS (EI, 70 eV) m/z 410, 408, and 406 ($M^{+\bullet}$, 1, 2, and 1, respectively), 137 (18), 122 (20), 121 (100); HRMS $M^{+\bullet}$ calcd for $C_{14}H_{16}{}^{79}Br_2O_4$ 405.9415, found 405.9400.

Compound 10. A magnetically stirred solution of bromohydrin **8** (1.10 g, 2.70 mmol) in methanol (20 mL) maintained at 18 °C was treated with freshly prepared sodium methoxide (730 mg, 13.5 mmol) and the resulting solution stirred at 18 °C for 6 h and then concentrated under reduced pressure. The residue thus obtained was dissolved in ethyl acetate (100 mL) and the solution so-formed washed with NH_4Cl (1 × 30 mL of a saturated aqueous solution). The separated organic layer was then dried (Na_2SO_4) before being filtered and concentrated under reduced pressure. The ensuing light yellow oil was subjected to flash chromatography (silica, 1:1 v/v ethyl acetate/hexane elution), and concentration of the appropriate fractions (R_f = 0.6) afforded alcohol **10** (800 mg, 82%) as a clear, colorless oil: $[\alpha]^{20}_D$ −60.8 (c 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 6.26 (d, J = 3.4 Hz, 1H), 4.78 (d, J = 11.2 Hz, 1H), 4.67 (d, J = 11.2 Hz, 1H), 4.25 (dd, J = 8.7 and 4.4 Hz, 1H), 3.98 (dd, J = 4.2 and 1.8 Hz, 1H), 3.94−3.91 (complex m, 2H), 3.81 (s, 3H), 3.43 (s, 3H), 2.95 (d, J = 8.8 Hz, 1H), 2.82 (d, J = 4.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 129.8, 129.7, 128.2, 127.1, 114.0, 79.5, 76.5, 73.2, 71.4, 71.1, 57.3, 55.3; IR ν_{max} 3434, 2932, 2834, 1611, 1514, 1463, 1344, 1302, 1249, 1175, 1094, 1033, 967, 827 cm^{-1}; MS (EI, 70 eV) m/z 360 and 358 ($M^{+\bullet}$, both 1), 137 (10), 122 (20), 121 (100); HRMS $M^{+\bullet}$ calcd for $C_{15}H_{19}{}^{79}BrO_5$ 358.0416, found 358.0413.

Compound 12. A magnetically stirred solution of alcohol **10** (1.90 g, 5.29 mmol), 2-hydroxyphenylboronic acid pinacol ester (**11**) (1.40 g, 6.40 mmol), $PdCl_2$dppf·CH_2Cl_2 (360 mg, 0.44 mmol), and triethylamine (10 mL) in THF/water (36 mL of a 9:1 v/v mixture) was purged with nitrogen for 0.5 h and then heated at 70 °C for 1 h before being cooled, poured into water (50 mL), and extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with brine (1 × 40 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing light yellow oil was subjected to flash chromatography (silica, 2:3 v/v ethyl acetate/hexane elution), and concentration of the relevant fractions (R_f = 0.3) afforded phenol **12** (1.60 g, 80%) as a clear, colorless oil: $[\alpha]^{20}_D$ −12.4 (c 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (broad s, 1H), 7.31 (d, J = 8.5 Hz, 2H), 7.24−7.20 (complex m, 1H), 7.09 (dd, J = 7.6 and 1.6 Hz, 1H), 6.92−6.87 (complex m, 3H), 6.85−6.81 (complex m, 1H), 6.07 (d, J = 4.3 Hz, 1H), 4.71 (d, J = 11.0 Hz, 1H), 4.62 (d, J = 11.0 Hz, 1H), 4.50 (m, 1H), 4.23 (m, 1H), 4.01 (m, 1H), 3.83 (m, 1H), 3.79 (s, 3H), 3.47 (s, 3H), 3.19 (broad s, 1H) (signal due to one proton obscured or overlapping); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 154.6, 139.8, 130.6, 129.9, 129.8, 129.5, 127.4, 127.0, 119.7, 117.2, 114.0, 78.3, 73.5, 70.9, 69.8, 68.1, 57.6, 55.3; IR ν_{max} 3291, 2933, 1611, 1513, 1485, 1357, 1301, 1248, 1175, 1091, 1032, 963, 826, 755 cm^{-1}; MS (EI, 70 eV) m/z 372 ($M^{+\bullet}$, 2), 160 (15), 122 (20), 121 (100); HRMS $M^{+\bullet}$ calcd for $C_{21}H_{24}O_6$ 372.1573, found 372.1572.

Compound 13. A magnetically stirred solution of Ph_3P (420 mg, 1.61 mmol) in dry THF (10 mL) was treated with DEAD (250 μL, 1.61 mmol), the resulting solution stirred at 18 °C for 0.17 h, and then a solution of phenol **12** (600 mg, 1.61 mmol) in THF (5 mL) was added dropwise. The ensuing mixture was stirred at 18 °C for 1 h before being concentrated under reduced pressure, and the resulting light yellow oil was subjected to flash chromatography (silica, 1:3 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions (R_f = 0.4) afforded compound **13** (500 mg, 88%) as a clear, colorless oil: $[\alpha]^{20}_D$ −65.2 (c 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 3H), 7.22 (m, 1H), 6.94−6.90 (complex m, 4H), 5.86 (t, J = 3.1 Hz, 1H), 5.26 (dt, J = 8.9 and 2.3 Hz, 1H), 4.95 (d, J = 11.3 Hz, 1H), 4.72 (d, J = 11.3 Hz, 1H), 4.17 (m, 1H), 4.03 (m, 1H), 3.83 (m, 1H), 3.82 (s, 3H), 3.45 (s, 3H), 2.59 (d, J = 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 159.4, 139.3, 130.6, 130.1, 129.7, 124.7, 121.5, 121.2, 113.9, 113.0, 110.9, 83.8, 80.2, 76.7, 72.1, 69.9, 57.8, 55.3; IR ν_{max} 3434, 2904, 1610, 1513, 1462, 1303, 1249, 1083, 1032, 952, 818, 751 cm^{-1}; MS (EI, 70 eV) m/z 354 ($M^{+\bullet}$, 1), 295 (10), 233 (10), 175 (25), 174 (100), 131 (20), 122 (20), 121 (85); HRMS $M^{+\bullet}$ calcd for $C_{21}H_{22}O_5$ 354.1467, found 354.1464.

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Compound 14. A magnetically stirred solution of alcohol **13** (300 mg, 0.85 mmol) in dry THF (10 mL) maintained at 0 °C was treated with NaH (51 mg of a 60% suspension in mineral oil, 1.27 mmol). After 0.5 h, the reaction mixture was treated with β-methoxyethoxymethyl chloride (146 μL, 1.27 mmol) and then stirred at 18 °C for 16 h before being quenched with water (30 mL; CAUTION: evolution of hydrogen gas). The separated aqueous layer was extracted with ethyl acetate (3 × 40 mL), and the combined organic phases were washed with brine (1 × 50 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting light yellow oil was subjected to flash chromatography (silica, 1:3 v/v ethyl acetate/hexane elution) to afford, after concentration of the appropriate fractions (R_f = 0.4 in 1:3 v/v ethyl acetate/hexane), tris-ether **14** (300 mg, 80%) as a clear, colorless oil: $[\alpha]^{20}_D$ −75.2 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.34 (complex m, 3H), 7.20(m, 1H), 6.93−6.87 (complex m, 4H), 5.81 (m, 1H), 5.35 (dm, *J* = 9.2 Hz, 1H), 4.95 (d, *J* = 6.9 Hz, 1H), 4.88 (d, *J* = 11.5 Hz, 1H), 4.84 (d, *J* = 6.9 Hz, 1H), 4.69 (d, *J* = 11.5 Hz, 1H), 4.24 (m, 1H), 4.03 (m, 1H), 3.89 (dd, *J* = 9.2 and 2.5 Hz, 1H), 3.80 (s, 3H), 3.76−3.73 (complex m, 2H), 3.54−3.48 (complex m, 2H), 3.43 (s, 3H), 3.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 159.1, 140.9, 130.5, 129.3, 125.0, 121.4, 121.0, 113.7, 112.8, 110.9, 95.7, 84.0, 79.3, 76.3, 74.1, 71.9, 71.6, 67.1, 59.0, 57.8, 55.2 (signal due to one carbon obscured over overlapping); IR ν_{max} 2904, 2890, 2835, 1674, 1611, 1514, 1463, 1362, 1303, 1248, 1081, 1019, 947, 820, 752 cm^{-1}; MS (EI, 70 eV) *m*/*z* 442 ($M^{+\bullet}$, <1%), 268 (5), 198 (10), 174 (27), 162 (15), 122 (19), 121 (100); HRMS (M + Na)$^+$ calcd for $C_{25}H_{30}O_7$ 465.1889, found 465.1890.

Compound 16. *Step i.* A magnetically stirred solution of compound **14** (900 mg, 2.03 mmol) in dry dichloromethane (40 mL) maintained at 0 °C was treated, in portions, with *m*-CPBA (550 mg of ca. 77% material, 2.43 mmol) and the resulting mixture warmed to 18 °C over 14 h and then diluted with $NaHCO_3$ (50 mL of a saturated aqueous solution). The separated aqueous phase was extracted with dichloromethane (3 × 30 mL), and the combined organic phases were then dried (Na_2SO_4) before being filtered and concentrated under reduced pressure. The resulting light yellow oil (presumed to be comprised largely of alcohol **15**) was immediately subjected to the next step of the reaction sequence.

Step ii. Dimethyl sulfoxide (1.10 mL, 15.5 mmol) was added dropwise to a magnetically stirred solution of oxalyl chloride (650 μL, 7.75 mmol) in dry dichloromethane (10 mL) maintained at −78 °C. The ensuing mixture was stirred at this temperature for 0.08 h, and then a solution of the oil obtained from *step i* in dichloromethane (20 mL) was added. The ensuing mixture was stirred at −78 °C for a further 0.33 h, treated with triethylamine (6.5 mL, 46.7 mmol), and allowed to stir for a further 0.66 h before being poured into brine (50 mL) and extracted with dichloromethane (3 × 40 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure, and the ensuing light yellow oil was subjected to flash chromatography (silica, 1:3 v/v ethyl acetate/hexane elution). Concentration of the relevant fractions (R_f = 0.2) afforded ketone **16** (650 mg, 70% from **14**) as a clear, colorless oil: $[\alpha]^{20}_D$ −131.4 (*c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (m, 1H), 7.55 (m, 1H), 7.40−7.33 (complex m, 4H), 6.92−6.89 (complex m, 2H), 5.07 (d, *J* = 3.6 Hz, 1H), 4.90−4.79 (complex m, 4H), 4.35 (dd, *J* = 7.9 and 3.6 Hz, 1H), 4.25 (d, *J* = 7.9 Hz, 1H), 3.81 (s, 3H), 3.70−3.67 (complex m, 2H), 3.65 (s, 3H), 3.51−3.48 (complex m, 2H), 3.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8, 165.6, 159.6, 155.8, 129.9, 129.8, 129.2, 126.0, 124.9, 123.1, 122.4, 113.9, 111.6, 95.7, 82.7, 77.2, 72.6, 71.6, 69.9, 67.2, 60.3, 59.0, 55.3; IR ν_{max} 2904, 2896, 2834, 1687, 1612, 1514, 1448, 1361, 1302, 1248, 1116, 1097, 1031, 844, 754 cm^{-1}; MS (ESI, +ve) *m*/*z* 479 [(M + Na$^+$), 100]; HRMS (M + Na)$^+$ calcd for $C_{25}H_{28}O_8$ 479.1682, found 479.1682.

Compound 17. A magnetically stirred mixture of ketone **16** (640 mg, 1.40 mmol) in dichloromethane/water (42 mL of a 20:1 v/v mixture) was treated with DDQ (380 mg, 1.68 mmol) and stirring continued at 18 °C for 20 h. After this time, the reaction mixture was poured into water (20 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic phases were washed with brine (1 × 40 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting light yellow oil was subjected to flash chromatography (silica, 3:2 v/v ethyl acetate/hexane elution) to afford, after concentration of the relevant fractions (R_f = 0.3 in 1:1 v/v ethyl acetate/hexane), alcohol **17** (380 mg, 81%) as a clear, colorless oil: $[\alpha]^{20}_D$ −31.9 (*c* 0.92, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (m, 1H), 7.55 (m, 1H), 7.40−7.32 (complex m, 2H), 5.40 (dd, *J* = 6.9 and 3.6 Hz, 1H), 4.95 (d, *J* = 7.5 Hz, 1H), 4.91 (d, *J* = 7.5 Hz, 1H), 4.32 (d, *J* = 6.9 Hz, 1H), 4.26 (dd, *J* = 7.5 and 3.6 Hz, 1H), 4.22 (d, *J* = 7.5 Hz, 1H), 3.86 (m, 1H), 3.76 (m, 1H), 3.63 (s, 3H), 3.62−3.56 (complex m, 2H), 3.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.4, 165.7, 155.8, 126.0, 124.8, 123.1, 122.3, 115.5, 111.7, 97.0, 82.1, 81.3, 71.6, 68.2, 64.4, 59.9, 59.0; IR ν_{max} 3400, 2896, 2830, 1683, 1603, 1483, 1448, 1245, 1200, 1096, 1044, 1022, 978, 844, 754 cm^{-1}; MS (ESI, +ve) *m*/*z* 359 [(M + Na)$^+$, 100]; HRMS (M + H)$^+$ calcd for $C_{17}H_{20}O_7$ 337.1287, found 337.1288.

Compound 18. A magnetically stirred solution of alcohol **17** (200 mg, 0.59 mmol) in dry THF (10 mL) was treated with Ph_3P (190 mg, 0.71 mmol), α-chloroacetic acid (67 mg, 0.71 mmol), and DEAD (110 μL, 0.71 mmol). The resulting solution was stirred at 18 °C for 1 h and then concentrated under reduced pressure. The light yellow residue thus obtained was subjected to flash chromatography (silica, 1:3 v/v ethyl acetate/hexane elution) to afford, after concentration of the relevant fractions (R_f = 0.3), α-chloroacetate **18** (210 mg, 85%) as an amorphous, white powder: $[\alpha]^{20}_D$ +98.9 (*c* 0.65, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (m, 1H), 7.54 (m, 1H), 7.44−7.36 (complex m, 2H), 6.38 (d, *J* = 6.5 Hz, 1H), 4.94 (s, 2H), 4.38 (dd, *J* = 6.6 and 8.4 Hz, 1H), 4.34 (d, *J* = 15.4 Hz, 1H), 4.26 (d, *J* = 15.4 Hz, 1H), 4.01 (d, *J* = 8.4 Hz, 1H), 3.77 (m, 1H), 3.70 (s, 3H), 3.68 (m, 1H), 3.58−3.55 (complex m, 2H), 3.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.5, 166.8, 160.7, 156.1, 126.7, 125.1, 122.5, 122.4, 116.9, 111.9, 97.0, 84.6, 79.3, 71.6, 69.2, 68.1, 60.7, 59.1, 40.7; IR ν_{max} 2925, 2887, 1764, 1688, 1449, 1241, 1172, 1132, 1048, 1013, 957, 855, 763 cm^{-1}; MS (ESI, +ve) *m*/*z* 437 and 435 [(M + Na)$^+$, 30 and 100]; HRMS (M + Na)$^+$ calcd for $C_{19}H_{21}{}^{35}ClO_8$ 435.0823, found 435.0826.

Compound 1. *Step i.* A magnetically stirred solution of α-chloroacetate **18** (170 mg, 0.41 mmol) in dry dichloromethane (15 mL) was treated with zinc bromide (920 mg, 4.10 mmol). The resulting solution was stirred at 18 °C for 16 h and then quenched by $NaHCO_3$ (20 mL of a saturated aqueous solution). The separated aqueous layer was extracted with dichloromethane (3 × 20 mL), and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting light yellow oil, presumed to contain compound **19**, was immediately subjected to the next step of the reaction sequence.

Step ii. A magnetically stirred solution of product obtained from *step i* in methanol (20 mL) was treated with zinc acetate dihydrate (110 mg, 0.49 mmol) and the ensuing mixture stirred at 18 °C for 6 h and then concentrated under reduced pressure. The resulting white solid was subjected to flash chromatography (silica, 2:1 v/v ethyl acetate/hexane elution) to afford, after concentration of the relevant fractions (R_f = 0.6), compound **1**[1,12] (51 mg, 50% from **18**) as an amorphous, white powder: $[\alpha]^{20}_D$ −24.9 (*c* 1.2, MeOH) [lit.[1] $[\alpha]^{25}_D$ −21.9 (*c* 1.0, MeOH)]; ^{1}H NMR (400 MHz, CD_3OD) see Table 1; ^{13}C NMR (100 MHz, CD_3OD) see Table 1; IR ν_{max} 3512, 3228, 2945, 2912, 2878, 2842, 1682, 1591, 1483, 1352, 1279, 1133, 1024, 1003, 948, 861, 750 cm^{-1}; MS (ESI, +ve) *m*/*z* 271 [(M + Na)$^+$, 100]; HRMS (M + Na)$^+$ calcd for $C_{13}H_{12}O_5$ 271.0582, found 271.0583.

A sample of this material suitable for single-crystal X-ray analysis was grown from a dichloromethane/methanol solution, mp 220−222 °C.

Compound 22. A magnetically stirred mixture of *cis*-diol **21**[13,15] (5.70 g, 21.5 mmol) in dry THF (100 mL) maintained at 0 °C was treated with NaH (2.60 g of a 60% suspension in mineral oil, 64.5 mmol) and, after 0.5 h, with iodomethane (6.70 mL, 107.5 mmol). The ensuing mixture was stirred at 18 °C for 1 h and then quenched with water (100 mL) (CAUTION: evolution of hydrogen gas). The separated aqueous layer was extracted with ethyl acetate (3 × 40 mL), and the combined organic phases were washed with brine (1 × 50 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash

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chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) to afford, after concentration of the relevant fractions (R_f = 0.7 in 3:1 v/v ethyl acetate/hexane), acetonide **22** (6.20 g, 98%) as a clear, colorless oil: $[\alpha]^{20}_D$ −64.5 (*c* 0.55, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.26 (d, *J* = 3.5 Hz, 1H), 4.63 (d, *J* = 5.8 Hz, 1H), 4.48 (t, *J* = 5.8 Hz, 1H), 3.97 (m, 1H), 3.76 (dd, *J* = 5.8 and 3.3 Hz, 1H), 3.53 (s, 3H), 3.45 (s, 3H), 1.45 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.7, 123.7, 109.9, 78.0, 76.8, 75.5, 74.8, 59.3, 57.5, 27.6, 25.9; IR ν_{max} 2986, 2933, 2827, 1645, 1455, 1382, 1371, 1234, 1198, 1118, 1081, 1042, 1008, 935, 870, 849 cm^{-1}; MS (EI, 70 eV) *m*/*z* 294 and 292 ($M^{+\bullet}$, both 1), 279 and 277 (both 5), 115 (100); HRMS $M^{+\bullet}$ calcd for $C_{11}H_{17}{}^{79}BrO_4$ 292.0310, found 292.0307.

Compound 23. Acetonide **22** (1.20 g, 4.1 mmol) was treated with acetic acid/water (50 mL of a 7:3 v/v mixture) and the resulting solution heated at 70 °C for 14 h and then cooled and concentrated under reduced pressure. The light yellow residue thus obtained was subjected to flash chromatography (silica, ethyl acetate elution) to afford, after concentration of the relevant fractions (R_f = 0.5), diol **23** (1.00 g, 97%) as a clear, colorless oil: $[\alpha]^{20}_D$ −175.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.35 (d, *J* = 4.7 Hz, 1H), 4.40 (d, *J* = 4.7 Hz, 1H), 4.20 (dd, *J* = 9.0 and 4.3 Hz, 1H), 4.01 (t, *J* = 4.3 Hz, 1H), 3.65 (dd, *J* = 9.0 and 3.8 Hz, 1H), 3.50 (s, 3H), 3.46 (s, 3H), 3.11 (broad s, 1H), 3.05 (broad s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.3, 126.8, 77.2, 73.7, 71.8, 68.1, 58.1, 57.8; IR ν_{max} 3401, 2917, 2827, 1643, 1196, 1097, 1001, 916, 864 cm^{-1}; MS (ESI, +ve) *m*/*z* 277 and 275 [$(M + Na)^+$, 100 and 95]; HRMS $(M + Na)^+$ calcd for $C_8H_{13}{}^{79}BrO_4$ 274.9895, found 274.9898.

Compound 24. *Step i.* A magnetically stirred solution of diol **23** (3.00 g, 11.9 mmol) in dichloromethane (30 mL) maintained at 0 °C was treated with *p*-methoxybenzaldehyde dimethyl acetal (2.20 mL, 13.0 mmol) and *p*-toluenesulfonic acid monohydrate (80 mg, 0.42 mmol). The resulting solution was stirred at 0 °C for 2 h and then treated with $NaHCO_3$ (30 mL of a saturated aqueous solution). The separated aqueous layer was extracted with dichloromethane (2 × 20 mL), and the combined organic phases were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting light yellow oil, containing the PMP-acetal derived from substrate **23**, was immediately subjected to the next step of the reaction sequence.

Step ii. The acetal prepared as described above was immediately dissolved in anhydrous dichloromethane (100 mL) and the resulting magnetically stirred solution cooled to −78 °C while being maintained under nitrogen and then treated with a solution of DIBAl-H (60 mL of a 1 M solution in hexanes, 60 mmol). The mixture thus obtained was stirred at −78 °C for 6 h before being treated with potassium sodium tartrate (100 mL of saturated aqueous solution). The mixture so-formed was stirred at 18 °C for 14 h, and then the separated aqueous phase was extracted with dichloromethane (3 × 50 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure, and the ensuing oil was subjected to flash chromatography (silica, 1:3 v/v ethyl acetate/hexane elution) to afford, after concentration of the relevant fractions (R_f = 0.4), compound **24** (2.20 g, 50%) as clear, colorless oil: $[\alpha]^{20}_D$ −81.7 (*c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.28 (d, *J* = 4.2 Hz, 1H), 4.72 (d, *J* = 11.2 Hz, 1H), 4.62 (d, *J* = 11.2 Hz, 1H), 4.30 (t, *J* = 5.5 Hz, 1H), 4.03 (dd, *J* = 8.1 and 4.4 Hz, 1H), 3.95 (m, 1H), 3.81 (s, 3H), 3.67 (m, 1H), 3.50 (s, 3H), 3.43 (s, 3H), 2.83 (d, *J* = 5.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 129.7, 129.6, 129.2, 126.8, 114.0, 77.0, 76.1, 75.3, 73.7, 70.8, 59.1, 57.6, 55.3. IR ν_{max} 3434, 2934, 2835, 1612, 1586, 1514, 1463, 1302, 1248, 1175, 1102, 1033 cm^{-1}; MS (ESI, +ve) *m*/*z* 397 and 395 [$(M + Na)^+$, 100 and 97]; HRMS $(M + Na)^+$ calcd for $C_{16}H_{21}{}^{79}BrO_5$ 395.0470, found 395.0475.

Compound 25. A magnetically stirred solution of tris-ether **24** (1.90 g, 5.1 mmol), 2-hydroxyphenylboronic acid pinacol ester (**11**) (1.10 g, 5.1 mmol), $PdCl_2$dppf·CH_2Cl_2 (290 mg, 0.35 mmol), and triethylamine (10 mL) in THF/water (36 mL of a 9:1 v/v mixture) was purged with nitrogen for 0.5 h and then heated at 70 °C for 2 h before being cooled, poured into water (50 mL), and extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with brine (1 × 40 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing light yellow oil was subjected to flash chromatography (silica, 1:3 v/v ethyl acetate/hexane elution), and concentration of the relevant fractions (R_f = 0.3) afforded phenol **25** (1.60 g, 81%) as a clear, colorless oil: $[\alpha]^{20}_D$ −29.7 (*c* 1.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (s, 1H), 7.30 (d, *J* = 8.7 Hz, 2H), 7.22 (m, 1H), 7.03 (dd, *J* = 7.6 and 1.7 Hz, 1H), 6.91 (dd, *J* = 8.1 and 1.0 Hz, 1H), 6.82−6.78 (complex m, 3H), 6.11 (d, *J* = 5.1 Hz, 1H), 4.84 (d, *J* = 10.6 Hz, 1H), 4.53 (d, *J* = 10.6 Hz, 1H), 4.28 (broad s, 1H), 4.12 (dd, *J* = 5.1 and 4.2 Hz, 1H), 4.07 (dd, *J* = 3.7 and 1.8 Hz, 1H), 3.94 (m, 1H), 3.83 (m, 1H), 3.67 (s, 3H), 3.62 (s, 3H), 3.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 154.7, 139.4, 130.7, 129.9, 129.7(3), 129.7(0), 127.4, 119.6, 117.1, 113.9, 77.6, 76.0, 74.0, 73.5, 69.7, 58.7, 58.2, 55.1 (signal due to one carbon obscured or overlapping); IR ν_{max} 3204, 2934, 2824, 1613, 1575, 1514, 1486, 1466, 1287, 1250, 1120, 1090, 1019 cm^{-1}; MS (EI, 70 eV) *m*/*z* 386 ($M^{+\bullet}$, 1), 192 (13), 160 (20), 122 (16), 121 (100); HRMS $M^{+\bullet}$ calcd for $C_{22}H_{26}O_6$ 386.1723, found 386.1729.

Compound 26. A magnetically stirred solution of Ph_3P (1.05 g, 4.0 mmol) in dry THF (5 mL) was treated with DEAD (620 μL, 4.0 mmol), the resulting solution was stirred at 18 °C for 0.17 h, and then a solution of phenol **25** (1.30 g, 3.37 mmol) in THF (15 mL) was added dropwise. The ensuing reaction mixture was stirred at 18 °C for 2 h before being concentrated under reduced pressure. The resulting light yellow oil was subjected to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) to afford, after concentration of the appropriate fractions (R_f = 0.7 in 1:3 v/v ethyl acetate/hexane), compound **26** (1.10 g, 89%) as a clear, colorless oil: $[\alpha]^{20}_D$ −89.5 (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.3 Hz, 2H), 7.37 (m, 1H), 7.22 (m, 1H), 6.94−6.89 (complex m, 4H), 6.04 (t, *J* = 3.2 Hz, 1H), 4.93 (ddd, *J* = 7.4, 3.2, and 1.5 Hz, 1H), 4.89 (d, *J* = 8.8 Hz, 1H), 4.83 (d, *J* = 8.8 Hz, 1H), 4.13 (m, 1H), 3.97 (t, *J* = 7.4 Hz, 2H), 3.81 (s, 3H), 3.54 (s, 3H), 3.52 (s, 3H), 3.51 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 159.2, 138.8, 130.7, 130.6, 129.6, 124.3, 121.5, 121.2, 113.8, 113.7, 110.9, 87.3, 81.3, 79.0, 76.6, 73.1, 58.8, 57.9, 55.3; IR ν_{max} 2931, 2833, 1611, 1513, 1463, 1302, 1248, 1174, 1118, 1086, 1031 cm^{-1}; MS (EI, 70 eV) *m*/*z* 368 ($M^{+\bullet}$, 1), 295 (10), 194 (20), 174 (40), 122 (20), 121 (100); HRMS $M^{+\bullet}$ calcd for $C_{22}H_{24}O_5$ 368.1624, found 368.1622.

Compound 28. *Step i.* A magnetically stirred solution of compound **26** (300 mg, 0.81 mmol) in dry dichloromethane (10 mL) maintained at 0 °C was treated, in portions, with *m*-CPBA (180 mg of ca. 77% material, 0.81 mmol), and the resulting mixture was warmed to 18 °C and then stirred at this temperature for 14 h before being diluted with $NaHCO_3$ (15 mL of a saturated aqueous solution). The separated aqueous phase was extracted with dichloromethane (3 × 20 mL), and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting light yellow oil, presumed to contain allylic alcohol **27**, was immediately subjected to the next step of the reaction sequence.

Step ii. Dimethyl sulfoxide (440 μL, 6.2 mmol) was added dropwise to a magnetically stirred solution of oxalyl chloride (260 μL, 3.1 mmol) in dry dichloromethane (4 mL) maintained at −78 °C. The ensuing mixture was stirred at this temperature for 0.08 h, and then a solution of the product obtained from *step i* in dichloromethane (10 mL) was added. The ensuing mixture was stirred at −78 °C for a further 0.33 h and then treated with triethylamine (2.60 mL, 18.7 mmol) and allowed to stir for a further 0.66 h before being poured into brine (30 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure, and the ensuing light yellow oil subjected to flash chromatography (silica, 1:3 v/v ethyl acetate/hexane elution). Concentration of the relevant fractions (R_f = 0.4) afforded ketone **28** (190 mg, 61% from **26**) as a clear, colorless oil: $[\alpha]^{20}_D$ −116.9 (*c* 3.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (m, 1H), 7.55 (m, 1H), 7.40−7.36 (complex m, 4H), 6.92 (d, *J* = 8.7 Hz, 2H), 4.95−4.75 (complex m, 3H), 4.40 (d, *J* = 2.4 Hz, 1H), 4.07 (dd, *J* = 4.3 and 2.4 Hz, 1H), 3.82 (s, 3H), 3.65 (s, 3H), 3.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.3, 164.8, 159.6, 155.9, 129.8, 129.2, 125.9, 124.7, 123.1, 122.3, 116.1, 114.0, 111.6, 83.1, 82.4, 73.0, 71.0, 59.6, 59.4, 55.2; IR ν_{max} 2934, 2834, 1701, 1612, 1587, 1514, 1483, 1447,

1303, 1251, 1174, 1131, 1110, 1076, 1034 cm^{-1}; MS (EI, 70 eV) *m*/*z* 382 ($M^{+\bullet}$, 10), 294 (20), 261 (20), 245 (20), 173 (30), 121 (100); HRMS $M^{+\bullet}$ calcd for $C_{22}H_{22}O_6$ 382.1416, found 382.1415.

Compound 29. A magnetically stirred mixture of ketone **28** (380 mg, 0.99 mmol) in dichloromethane/water (21 mL of a 20:1 v/v mixture) maintained at 18 °C was treated with DDQ (250 mg, 1.09 mmol), and the resulting mixture was stirred at 18 °C for 24 h, poured into water (20 mL), and extracted with dichloromethane (3 × 30 mL). The combined organic phases were washed with brine (1 × 40 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting light yellow oil was subjected to flash chromatography (silica, 1:2 v/v ethyl acetate/hexane elution) to afford, after concentration of the relevant fractions (R_f = 0.1 in 1:3 v/v ethyl acetate/hexane), alcohol **29** (220 mg, 85%) as a clear, colorless oil: $[\alpha]^{20}_D$ −131.9 (*c* 0.47, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (m, 1H), 7.53 (m, 1H), 7.40−7.38 (complex m, 2H), 5.30 (d, *J* = 6.0 Hz, 1H), 4.25 (broad s, 1H), 3.90 (m, 1H), 3.60 (s, 3H), 3.57 (s, 3H), 3.00 (broad s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.5, 165.8, 155.9, 126.1, 124.9, 123.0, 122.2, 115.4, 111.7, 84.6, 81.7, 65.8, 59.1, 58.9; IR ν_{max} 3412, 2934, 2832, 1693, 1599, 1483, 1447, 1280, 1204, 1106, 1072, 1024 cm^{-1}; MS (EI, 70 eV) *m*/*z* 262 ($M^{+\bullet}$, 35), 247 (30), 230 (53), 229 (50), 201 (30), 174 (100), 153 (60), 146 (80), 145 (47); HRMS $M^{+\bullet}$ calcd for $C_{14}H_{14}O_5$ 262.0841, found 262.0843.

Compound 30. A magnetically stirred solution of alcohol **29** (150 mg, 0.57 mmol) in dry THF (10 mL) was treated with Ph_3P (180 mg, 0.69 mmol), α-chloroacetic acid (65 mg, 0.69 mmol), and DEAD (110 μL, 0.69 mmol). The resulting solution was stirred at 18 °C for 1 h and then concentrated under reduced pressure. The light yellow residue thus obtained was subjected to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) to afford, after concentration of the relevant fractions (R_f = 0.4 in 1:3 v/v ethyl acetate/hexane), α-chloroacetate **30** (140 mg, 74%) as a clear, colorless oil: $[\alpha]^{20}_D$ +101.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 8.04 (m, 1H), 7.51 (m, 1H), 7.41−7.34 (complex m, 2H), 6.52 (d, *J* = 3.8 Hz, 1H), 4.40 (dd, *J* = 3.8 and 2.2 Hz, 1H), 4.30 (s, 2H), 4.11 (m, 1H), 3.71 (s, 3H), 3.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.3, 166.9, 160.3, 155.9, 126.4, 125.0, 122.8, 122.3, 116.8, 111.7, 84.4, 81.2, 68.1, 61.1, 59.9, 40.6; IR ν_{max} 2938, 2837, 1756, 1698, 1590, 1483, 1448, 1254, 1163, 1138, 1098, 1055 cm^{-1}; MS (EI, 70 eV) *m*/*z* 340 and 338 ($M^{+\bullet}$, 3 and 10), 275 (20), 261 (70), 245 (90), 229 (60), 174 (55), 173 (60), 153 (100), 105 (62); HRMS $(M + Na)^+$ calcd for $C_{16}H_{15}{}^{35}ClO_6$ 361.0455, found 361.0455.

Compound 2. A magnetically stirred solution of α-chloroacetate **30** (140 mg, 0.32 mmol) in methanol (15 mL) was treated with zinc acetate dihydrate (110 mg, 0.50 mmol) and the ensuing mixture stirred at 18 °C for 12 h then concentrated under reduced pressure. The resulting white solid was subjected to flash chromatography (silica, 1:2 v/v ethyl acetate/hexane elution) to afford, after concentration of the relevant fractions (R_f = 0.6 in 1:1 v/v ethyl acetate/hexane), compound **2** (90 mg, 81%) as an amorphous, white powder: $[\alpha]^{20}_D$ +51.9 (*c* 0.36, MeOH) or −54.5 (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ see Table S1 (Supporting Information); ^{13}C NMR (100 MHz, $CDCl_3$) δ see Table S1 (Supporting Information); IR ν_{max} 3304, 2991, 2940, 2837, 1693, 1588, 1481, 1447, 1138, 1115, 1101, 1081, 1051, 1029, 1010 cm^{-1}; MS (EI, 70 eV) *m*/*z* 262 ($M^{+\bullet}$, 10), 174 (20), 153 (100), 105 (50); HRMS $M^{+\bullet}$ calcd for $C_{14}H_{14}O_5$ 262.0841, found 262.0841.

A sample of this material suitable for single-crystal X-ray analysis was grown from a dichloromethane/methanol solution, mp 166−168 °C.

Compound 31. The title compound was prepared as previously described[3] from diol **5** using the 12-step reaction sequence show in Scheme 3. The spectral data obtained on compound **31** have been presented elsewhere[3] and compared favorably (see Table 2) with those reported[1] for the natural product ribisin C.

Compound 44. A magnetically stirred mixture of phenol **43**[17] (14.0 g, 60.6 mmol) in dry THF (150 mL) maintained at 0 °C was treated with NaH (2.90 g of a 60% suspension in oil, 72.7 mmol). After 0.5 h, the reaction mixture was treated with chloromethyl methyl ether (4.90 mL, 64.5 mmol) and then stirred at 18 °C for 48 h before being quenched with water (100 mL, CAUTION: evolution of hydrogen gas). The separated aqueous layer was extracted with diethyl ether (3 × 40 mL), and the combined organic phases were washed with brine (1 × 50 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 5:95 v/v diethyl ether/hexane elution) to afford, after concentration of the relevant fractions (R_f = 0.8), bromide **44** (16.0 g, 96%) as a clear, colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, *J* = 7.8 Hz, 1H), 6.92−6.84 (complex m, 2H), 5.18 (s, 2H), 4.54 (septet, *J* = 6.0 Hz, 1H), 3.67 (s, 3H), 1.34 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 144.5, 125.1, 124.9, 118.1, 114.8, 98.6, 71.4, 58.0, 22.2; IR ν_{max} 2977, 2931, 1581, 1465, 1384, 1288, 1261, 1231, 1206, 1159, 1111, 1072, 963, 879 cm^{-1}; MS (EI, 70 eV) *m*/*z* 276 and 274 ($M^{+\bullet}$, 99 and 100), 234 and 232 (38 and 41), 204 (67), 202 (83), 189 and 187 (both 60), 153 (50), 51 (57); HRMS $M^{+\bullet}$ calcd for $C_{11}H_{15}{}^{79}BrO_3$ 274.0205, found 274.0198.

Compound 40. *Step i.* A magnetically stirred mixture of bromide **44** (4.0 g, 14.5 mmol) in dry THF (50 mL) maintained at −78 °C was treated with a *n*-BuLi solution (11.0 mL of a 1.6 M solution in THF, 17.6 mmol). After 1 h, the reaction mixture was treated with triisopropyl borate (6.70 mL, 29.0 mmol) and then stirred at 18 °C for 14 h before being quenched with HCl (20 mL of a 10% w/v aqueous solution). The separated aqueous layer was extracted with ethyl acetate (3 × 50 mL), and the combined organic phases were washed with brine (1 × 50 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained, which is presumed to contain boronic acid **45**, was subjected directly to *step ii* of the reaction sequence.

Step ii. A magnetically stirred mixture of the product obtained from *step i* in dry CH_3CN (40 mL) maintained at 0 °C was treated with sodium iodide (2.17 g, 14.5 mmol) and chlorotrimethylsilane (1.84 mL, 14.5 mmol). The resulting solution was warmed to 18 °C over 4 h and then treated with $Na_2S_2O_3$ (50 mL of a saturated aqueous solution). The separated aqueous layer was extracted with ethyl acetate (3 × 50 mL), and the combined organic phases were washed with brine (1 × 50 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was immediately subjected to *step iii* of the reaction sequence.

Step iii. A magnetically stirred mixture of the product obtained from *step ii* in benzene (50 mL) was treated with pinacol (3.44 g, 29.0 mmol), and the solution thus obtained heated at reflux for 2 h in an apparatus fitted with a Dean−Stark trap. The cooled reaction was treated with water (20 mL) and the separated aqueous layer extracted with ethyl acetate (3 × 40 mL). The combined organic phases were washed with brine (1 × 50 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:5 v/v diethyl ether/hexane elution) to afford, after concentration of the relevant fractions (R_f = 0.6), boronic acid pinacol ester **40** (1.80 g, 45% from **44**) as an amorphous, white powder: $[\alpha]^{20}_D$ −64.5 (*c* 0.55, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.21 (m, 1H), 6.98 (dd, *J* = 7.5 and 1.4 Hz, 1H), 6.79 (t, *J* = 7.5 Hz, 1H), 4.50 (septet, *J* = 6.1 Hz, 1H), 1.33(8) (s, 12H), 1.33(6) (d, *J* = 6.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 145.2, 127.7, 120.2, 119.5, 84.3, 71.5, 24.8, 22.1 (signal due to one carbon obscured or overlapping); IR ν_{max} 3436, 2978, 2933, 1615, 1577, 1456, 1368, 1308, 1272, 1243, 1167, 1113, 1076, 985, 896, 856, 839, 826, 745, 678 cm^{-1}; MS (EI, 70 eV) *m*/*z* 278 ($M^{+\bullet}$, 30), 180 (21), 179 (100), 178 (50), 136 (40); HRMS $M^{+\bullet}$ calcd for $C_{15}H_{23}{}^{11}BO_4$ 278.1689, found 278.1689.

Compound 46. A magnetically stirred solution of compound **36** (2.00 g, 5.36 mmol), ester **40** (1.80 g, 6.70 mmol), $PdCl_2dppf{\cdot}CH_2Cl_2$ (310 mg, 0.38 mmol), and triethylamine (10 mL) in THF/water (36 mL of a 9:1 v/v mixture) was purged with nitrogen for 0.5 h and then heated at 70 °C for 1 h before being cooled, poured into water (50 mL), and extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with brine (1 × 40 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing light yellow oil was subjected to flash chromatography (silica, 1:2 v/v ethyl acetate/hexane elution) and concentration of the relevant fractions (R_f = 0.7 in 1:1 v/v ethyl acetate/hexane) afforded phenol **46** (2.20 g,

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92%) as a clear, colorless oil: $[\alpha]^{20}_{D}$ −117.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.6 Hz, 2H), 7.20 (broad s, 1H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.81−6.73 (complex m, 3H), 5.94 (d, *J* = 3.3 Hz, 1H), 4.79−4.73 (complex m, 3H), 4.54 (septet, *J* = 6.1 Hz, 1H), 4.13 (m, 1H), 4.05 (m, 1H), 3.80 (s, 3H), 3.65 (m, 1H), 3.54 (s, 3H), 3.47 (s, 3H), 1.35 (d, *J* = 6.1 Hz, 6H) (signal due to one proton obscured or overlapping); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 145.1, 144.6, 140.3, 130.4, 129.5, 126.7, 125.4, 122.4, 119.2, 113.8, 113.7, 81.8, 77.1, 75.0, 72.2, 71.6, 68.2, 58.7, 57.1, 55.2, 22.2(0), 22.1(9); IR ν_{max} 3504, 2976, 2932, 1611, 1582, 1513, 1464, 1464, 1354, 1247, 1173, 1110, 972, 824 cm^{-1}; MS (EI, 70 eV) *m*/*z* 444 ($M^{+\bullet}$, 5), 122 (22), 121 (100); HRMS $M^{+\bullet}$ calcd for $C_{25}H_{32}O_7$ 444.2148, found 444.2150.

Compound 47. A magnetically stirred solution of Ph_3P (1.42 g, 5.4 mmol) in dry THF (10 mL) was treated with DEAD (850 μL, 5.4 mmol), the resulting solution was stirred at 18 °C for 0.17 h, and then a solution of phenol **46** (2.0 g, 4.5 mmol) in THF (15 mL) was added dropwise. The ensuing reaction mixture was stirred at 18 °C for 1 h before being concentrated under reduced pressure. The resulting light yellow oil was subjected to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) to afford, after concentration of the appropriate fractions (R_f = 0.5 in 1:3 v/v ethyl acetate/hexane), compound **47** (1.80 g, 94%) as a clear, colorless oil: $[\alpha]^{20}_{D}$ −303.6 (*c* 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.7 Hz, 2H), 7.00 (m, 1H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.84−6.77 (complex m, 2H), 5.79 (m, 1H), 5.37 (m, 1H), 4.94 (d, *J* = 11.7 Hz, 1H), 4.72 (d, *J* = 11.7 Hz, 1H), 4.63 (septet, *J* = 6.1 Hz, 1H), 4.01 (m, 1H), 3.88 (dd, *J* = 9.2 and 2.3 Hz, 1H), 3.80 (s, 3H), 3.72 (m, 1H), 3.57 (s, 3H), 3.41 (s, 3H), 1.33 (d, *J* = 6.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 153.1, 143.1, 141.3, 130.8, 129.3, 126.8, 121.6, 119.9, 114.6, 113.7, 112.6, 84.5, 79.5, 78.3, 76.9, 72.6, 72.1, 59.5, 57.6, 55.3, 22.4; IR ν_{max} 2976, 2931, 1612, 1586, 1513, 1464, 1302, 1248, 1174, 1111, 1063, 989, 824 cm^{-1}; MS (EI, 70 eV) *m*/*z* 426 ($M^{+\bullet}$, 12), 273 (30), 121 (100); HRMS $M^{+\bullet}$ calcd for $C_{25}H_{30}O_6$ 426.2042, found 426.2041.

Compound 48. *Step i.* A magnetically stirred solution of compound **47** (1.00 g, 2.34 mmol) in dry dichloromethane (30 mL) maintained at 0 °C was treated, in portions, with *m*-CPBA (630 mg of ca. 77% material, 2.81 mmol) and the resulting mixture warmed to 18 °C and stirred at this temperature for 14 h before being diluted with $NaHCO_3$ (30 mL of a saturated aqueous solution). The separated aqueous phase was extracted with dichloromethane (3 × 30 mL), and the combined organic phases were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting light yellow oil, presumed to contain the alcohol precursor to ketone **48**, was immediately subjected to the next step of the reaction sequence.

Step ii. Dimethyl sulfoxide (1.10 mL, 15.5 mmol) was added dropwise to a magnetically stirred solution of oxalyl chloride (0.65 mL, 7.75 mmol) in dry dichloromethane (10 mL) maintained at −78 °C. The ensuing mixture was stirred at this temperature for 0.08 h, then a solution of the product obtained from *step i* in dichloromethane (30 mL) was added. The resulting mixture was stirred at −78 °C for a further 0.33 h, treated with triethylamine (6.50 mL, 46.7 mmol), and allowed to stir for a further 0.66 h before being poured into brine (20 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure and the ensuing light yellow oil subjected to flash chromatography (silica, 1:3 v/v ethyl acetate/hexane elution). Concentration of the relevant fractions (R_f = 0.1) afforded ketone **48** (600 mg, 58% from **47**) as a pale yellow oil: $[\alpha]^{20}_{D}$ −265.3 (*c* 0.67, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.28 (m, 1H), 6.96−6.92 (complex m, 3H), 5.08 (d, *J* = 3.5 Hz, 1H), 4.89 (d, *J* = 11.7 Hz, 1H), 4.83−4.76 (complex, 2H), 4.36 (d, *J* = 8.7 Hz, 1H), 3.88 (dd, *J* = 8.7 and 3.6 Hz, 1H), 3.84 (s, 3H), 3.75 (s, 3H), 3.55 (s, 3H), 1.46 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9, 164.8, 159.5, 146.3, 143.5, 130.0, 129.2, 125.7, 124.9, 116.8, 114.5, 113.8, 112.2, 82.5, 81.9, 72.4, 72.0, 68.4, 60.6, 58.8, 55.3, 22.2(3), 22.19(2); IR ν_{max} 2978, 2933, 2833, 1687, 1612, 1514, 1494, 1464, 1302, 1276, 1248, 1175, 1112, 1068, 1033, 920, 821 cm^{-1}; MS (EI, 70 eV) *m*/*z* 440 ($M^{+\bullet}$, 20), 352 (10), 231 (35), 189 (20), 122 (20), 121 (100); HRMS $M^{+\bullet}$ calcd for $C_{25}H_{28}O_7$ 440.1835, found 440.1826.

Compound 49. A magnetically stirred mixture of ketone **48** (600 mg, 1.36 mmol) in dichloromethane/water (21 mL of a 20:1 v/v mixture) was treated with DDQ (340 mg, 1.59 mmol). The ensuing mixture was stirred at 18 °C for 20 h and then was poured into water (20 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic phases were washed with brine (1 × 40 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting light yellow oil was subjected to flash chromatography (silica, 1:2 v/v ethyl acetate/hexane elution) to afford, after concentration of the relevant fractions (R_f = 0.4 in 1:1 v/v ethyl acetate/hexane), alcohol **49** (370 mg, 84%) as a white foam: $[\alpha]^{20}_{D}$ −132.9 (*c* 0.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.8 Hz, 1H), 7.28 (m, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 5.33 (d, *J* = 3.7 Hz, 1H), 4.82 (septet, *J* = 6.0 Hz, 1H), 4.19 (d, *J* = 7.0 Hz, 1H), 3.98 (dd, *J* = 7.0 and 3.7 Hz, 1H), 3.65 (s, 3H), 3.64 (s, 3H), 3.13 (broad s, 1H), 1.44 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.3, 164.8, 146.0, 143.6, 125.7, 124.9, 115.8, 114.1, 111.6, 82.0, 81.7, 71.6, 63.6, 59.9, 59.4, 22.0(9), 22.0(8); IR ν_{max} 3430, 2979, 2934, 2832, 1686, 1624, 1600, 1494, 1464, 1385, 1374, 1277, 1192, 1140, 1112, 1059, 1022, 988, 914, 820, 794 cm^{-1}; MS (EI, 70 eV) *m*/*z* 320 ($M^{+\bullet}$, 80), 278 (30), 246 (46), 245 (50), 232 (43), 190 (100), 162 (50), 134 (37); HRMS $M^{+\bullet}$ calcd for $C_{17}H_{20}O_6$ 320.1260, found 320.1262.

Compound 50. A magnetically stirred solution of alcohol **49** (310 mg, 0.97 mmol) in dry THF (20 mL) was treated with Ph_3P (280 mg, 1.06 mmol), α-chloroacetic acid (100 mg, 1.06 mmol), and DEAD (170 μL, 1.06 mmol). The resulting solution was stirred at 18 °C for 2 h and then concentrated under reduced pressure, and the light yellow residue thus obtained was subjected to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane elution). Concentration of the relevant fractions (R_f = 0.4 in 1:3 v/v ethyl acetate/hexane) then afforded α-chloroacetate **50** (320 mg, 84%) as an amorphous, white powder: $[\alpha]^{20}_{D}$ +15.4 (*c* 0.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.7 Hz, 1H), 7.26 (t, *J* = 7.7 Hz, 1H), 6.92 (d, *J* = 7.7 Hz, 1H), 6.32 (d, *J* = 5.4 Hz, 1H), 4.75 (septet, *J* = 6.0 Hz, 1H), 4.24−4.23 (complex m, 2H), 4.00−3.95 (complex m, 2H), 3.68 (s, 3H), 3.62 (s, 3H), 1.41 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.6, 166.6, 160.4, 146.3, 143.6, 126.0, 124.5, 117.2, 114.3, 112.6, 84.3, 82.4, 72.1, 68.4, 60.4(4), 60.4(3), 40.6, 22.1(2), 22.1(1); IR ν_{max} 2978, 2935, 2837, 1768, 1691, 1624, 1600, 1494, 1318, 1277, 1188, 1143, 1110, 1080, 1010, 921, 852, 789 cm^{-1}; MS (EI, 70 eV) *m*/*z* 398 and 396 ($M^{+\bullet}$, 23 and 50%), 277 (60), 261 (100), 245 (60), 190 (62), 189 (60); HRMS $M^{+\bullet}$ calcd for $C_{19}H_{21}{}^{35}ClO_7$ 396.0976, found 396.0973.

Compound 4. *Step i.* A magnetically stirred solution of α-chloroacetate **50** (180 mg, 0.45 mmol) in methanol (15 mL) was treated with zinc acetate dihydrate (120 mg, 0.54 mmol) and the ensuing mixture stirred at 18 °C for 4 h then concentrated under reduced pressure. The resulting white solid was treated with ethyl acetate (50 mL), and the suspension thus obtained was filtered through a short plug of TLC-grade silica gel and the filtrate concentrated under reduced pressure. The white solid thus obtained and presumed to contain compound **51**, was immediately subjected to the next step of the reaction sequence.

Step ii. A magnetically stirred solution of the product obtained from *step i* in dry dichloromethane (20 mL) maintained at −78 °C was treated with BBr_3 (0.5 mL of a 1 M solution in dichloromethane, 0.5 mmol). The resulting solution was stirred at −78 °C for 0.33 h, and then a further three aliquots of BBr_3 (3 × 0.5 mL of a 1 M solution in dichloromethane, 0.5 mmol) were added at 0.33 h intervals. A further 1 h after the addition of the last aliquot of BBr_3, the reaction mixture was quenched by careful addition of water (10 mL), the resulting mixture was warmed to 18 °C, and then the separated aqueous phase was extracted with dichloromethane (3 × 30 mL). The combined organic phases were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure, and the light yellow residue thus obtained subjected to flash chromatography (silica, 3:2 v/v ethyl acetate/hexane elution). Concentration of the relevant fractions (R_f = 0.6) then afforded compound **4**[1] (45 mg, 36% from **50**) as an amorphous, white

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powder: $[\alpha]^{20}_{D}$ −39.3 (*c* 0.8, MeOH) {lit.[1] $[\alpha]_{D}^{24}$ −22.0 (*c* 0.2, MeOH)}; ^{1}H NMR (400 MHz, CD_3OD) δ see Table 3; ^{13}C NMR (100 MHz, CD_3OD) δ see Table 3; IR ν_{max} 3306, 2942, 1679, 1597, 1493, 1332, 1250, 1178, 1142, 1110, 1050, 1018, 850, 789 cm^{-1}; MS (EI, 70 eV) *m*/*z* 278 ($M^{+\bullet}$, 50), 248 (38), (246 (36), 245 (40), 190 (100), 162 (70), 134 (60); HRMS $M^{+\bullet}$ calcd for $C_{14}H_{14}O_6$ 278.0790, found 278.0789.

A sample of this material suitable for single-crystal X-ray analysis was grown from a hexane/dichloromethane/methanol solution, mp 194−196 °C.

Compound 52. A magnetically stirred solution of alcohol **49** (0.10 g, 0.31 mmol) in dry dichloromethane (10 mL) maintained at −78 °C was treated with BBr_3 (0.35 mL of a 1 M solution in dichloromethane, 0.35 mmol), and then a further three aliquots of BBr_3 (3 × 0.5 mL of a 1 M solution in dichloromethane, 0.5 mmol) were added at 0.33 h intervals. A further 1 h after the addition of the last aliquot of BBr_3, the reaction mixture was quenched by careful addition of water (10 mL), the resulting mixture was warmed to 18 °C, the separated aqueous phase was extracted with dichloromethane (3 × 30 mL), and the combined organic phases dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The light yellow residue thus obtained was subjected to flash chromatography (silica, 3:2 v/v ethyl acetate/hexane elution) to afford, after concentration of the relevant fractions (R_f = 0.6), compound **52** (50 mg, 57%) as a white foam: $[\alpha]^{20}_{D}$ −78.1 (*c* 1, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ see Table S2 (Supporting Information); ^{13}C NMR (100 MHz, CD_3OD) δ see Table S2 (Supporting Information); IR ν_{max} 3339, 2932, 2838, 1680, 1599, 1493, 1334, 1178, 1098, 1052, 1021, 841, 801 cm^{-1}; MS (EI, 70 eV) *m*/*z* 278 ($M^{+\bullet}$, 60%), 246 (50), 245 (50), 190 (100), 162 (70), 134 (60); HRMS $M^{+\bullet}$ calcd for $C_{14}H_{14}O_6$ 278.0790, found 278.0789.

Crystallographic Studies. *Crystallographic Data. Compound 1:* $C_{13}H_{12}O_5{\cdot}H_2O$, M = 266.25, T = 200 K, orthorhombic, space group $P2_12_12_1$, Z = 4, a = 5.1685(2) Å, b = 10.4961(4) Å, c = 21.9445(7) Å; V = 1190.47(8) Å^3, D_x = 1.485 g cm^{-3}, 1615 unique data ($2\theta_{max}$ = 55°), R = 0.037 [for 1234 reflections with $I > 2.0\sigma(I)$]; R_w = 0.084 (all data), S = 0.99.

Compound 2: $C_{14}H_{14}O_5$, M = 262.26, T = 200 K, monoclinic, space group $P2_1$, Z = 2, a = 10.2259(6) Å, b = 4.7596(3) Å, c = 13.9296(8) Å; β = 108.834(3)°; V = 641.67(7) Å^3, D_x = 1.357 g cm^{-3}, 1278 unique data ($2\theta_{max}$ = 50°), R = 0.040 [for 1106 reflections with $I > 2.0\sigma(I)$]; R_w = 0.091 (all data), S = 1.02.

Compound 4: $C_{14}H_{14}O_6{\cdot}H_2O$, M = 296.28, T = 200 K, orthorhombic, space group $P2_12_12_1$, Z = 4, a = 4.7511(5) Å, b = 13.5474(10) Å, c = 20.9950(18) Å; V = 1351.3(2) Å^3, D_x = 1.456 g cm^{-3}, 1412 unique data ($2\theta_{max}$ = 49.8°), R = 0.071 [for 914 reflections with $I > 2.0\sigma(I)$]; R_w = 0.126 (all data), S = 1.01.

Structure Determinations. Images were measured on a CCD diffractometer (Mo Kα, graphite monochromator, λ = 0.71073 Å) and data extracted using the DENZO package.[21] Structure solutions were by direct methods (SIR92).[22] The structures of compounds **1**, **2**, and **4** were refined using the CRYSTALS program package.[23] Atomic coordinates, bond lengths and angles, and displacement parameters for compounds **1**, **2**, and **4** have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos. 981971, 981972, and 981973 for compounds **1**, **2**, and **4**, respectively). These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif.

■ ASSOCIATED CONTENT

Supporting Information

Crystallographic data (CIFs), anisotropic displacement ellipsoid plots derived from the single-crystal analyses of compounds **1**, **2**, and **4**; Tables S1 and S2 (comparison of the ^{13}C and ^{1}H NMR data recorded for compounds **2** and **52** with those reported for ribisins B and D, respectively) and Table S3 (comparison of the ^{13}C NMR data recorded for synthetically derived compound **4** at varying pH with those reported for ribisin D); ^{13}C and ^{1}H NMR spectra for compounds **1**, **2**, **4**, **8**, **10**, **12**−**14**, **16**−**18**, **22**−**26**, **28**−**30**, **40**, **44**, **46**−**50**, and **52**. This material is available free-of-charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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NOTE ADDED AFTER ASAP PUBLICATION

Scheme 5 contained an error in the version published ASAP February 28, 2014; the correct version reposted March 4, 2014.