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Asymmetric Synthesis and CD Investigation of the 1,4-Benzodioxane Lignans Eusiderins A, B, C, G, L, and M

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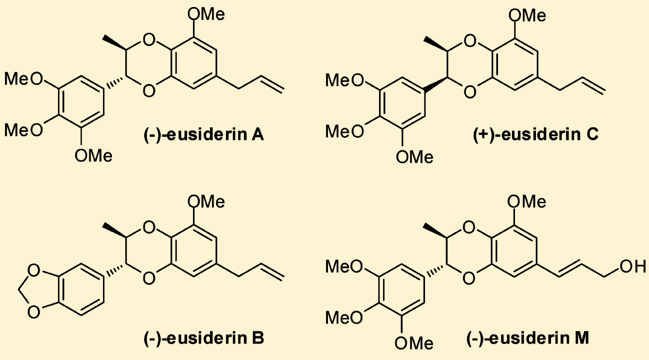
S Supporting Information

ABSTRACT: The enantioselective synthesis of (−)-eusiderins A (**1**), B (**2**), G (**25**), L (**23**), M (**5**) and (+)-eusiderin C (**20**) and a range of analogues was undertaken using an efficient, divergent synthesis all from a single chiral aldehyde **15**, which was derived from (*S*)-ethyl lactate **9**. A comprehensive set of NMR data along with ECD spectra and optical rotation measurements of the synthesized natural products and analogues were then obtained. This data confirmed the absolute stereochemistry of eusiderins A (**1**) and C (**20**) and for the first time gives the ECD and optical rotation for eusiderins B (**2**), G (**25**), L (**23**), and M (**5**) and a range of other substituted 1,4-benzodioxanes. This data will now allow for the determination of absolute stereochemistry of other members in this class of compound.



INTRODUCTION

Lignans are a class of secondary metabolites that are generally derived from the oxidative dimerization of two or more phenylpropane units.[1] Despite their common biosynthetic building blocks and resultant molecular backbone, lignans show vast structural diversity and are extensively distributed among and within members of the plant kingdom.[1−3]

A small but significant subgroup within the lignan class, 1,4-benzodioxane neolignans exhibit a diverse range of interesting pharmacological properties that lend them to be desirable synthetic targets. 1,4-Benzodioxane lignans have demonstrated cytotoxic, hepatoprotective and antimicrobial activities along with many others.[4−8] They have also been discovered to act as α- and β-blockers, with therapeutic potential as antihypertensive and antidepressant agents[9−14] and to inhibit 5-lipoxygenase, an antihyperglycemic target.[9,15]

1,4-Benzodioxanes lignans are thought to be formed by the phenolic coupling of two C_6C_3 units (Figure 1) through a three-step process, involving an enzymatically promoted phenol oxidation of the two C_6C_3 units, the coupling of the resulting radicals, and the cyclization step of the two quinone methides.[16] The last two steps may not be enzymatically controlled and as such will for the most part result in a mixture of stereo- and regio-isomers being formed. 1,4-Benzodioxane lignan natural products are therefore usually found as racemic mixtures.[16,17]

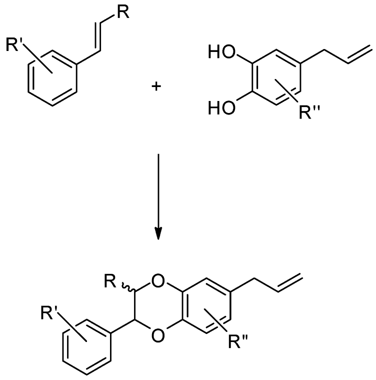


Figure 1. Proposed biosynthesis of 1,4-benzodioxane neolignans.

The eusiderin family, however is one of the few groups of 1,4-benzodioxanes that are found to be chiral in nature.[16] The first member of the eusiderin family, eusiderin A **1** was isolated by Hobbs et al.[18] from *Eusideroxylon zwageri*, and since then a further 12 eusiderins (B−M) have been isolated from an array of trees and plants. While the core structure remains constant among all eusiderins, within the 13 members there is variation (Figure 2). The main source of difference between eusiderins is the substitution on the appended (nonbenzodioxane) aromatic ring—although 3,4-methylenedioxy, 3,4-dimethoxy, and 4-hydroxy-3,5-dimethoxy substitution patterns, as shown in eusiderin B **2**, eusiderin D **3** and eusiderin E **4** respectively are seen, the most common is 3,4,5-trimethoxy as is exhibited by **1**, eusiderin M **5** and four other eusiderins. The second main point of variation is the allylic side chain. Once again, eusiderin A **1**, along with **2** and **3**, display the most common side chain—a terminal allyl group. Eusiderins E **4** and M **5** show examples of isomerized allylic group variations which are seen in naturally occurring compounds. While the more stable *trans* benzodiox-

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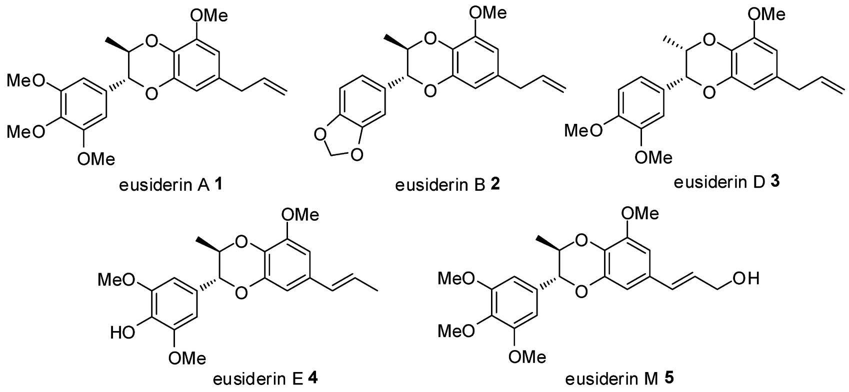


Figure 2. Structural diversity in the eusiderin family.

anes, for example, **1**, **2**, **4** and **5** are most often found in the natural products, *cis* benzodioxanes like **3** have also been isolated.

The eusiderins were found to be chiral by the use of ECD studies on some of the natural products,[16,19] however there has only been limited data given for these natural compounds including no optical rotation readings for all but one. ECD data have been used to assign absolute stereochemistry for members of the eusiderin family with comparison to a simplified 1,4-benzodioxane model which could not be used to determine the configuration of all eusiderins.[16] Complicating the assignment of absolute stereochemistry is the fact that for some eusiderins, such as eusiderin C, both enantiomers have been found in nature. There are also recent examples of other lignans which have used ECD studies to assign the absolute stereochemistry, that were later found to be incorrect.[20]

All of the previous syntheses of eusiderins are racemic,[5,9,21−24] mainly using an oxidative dimerization strategy, and have not allowed for the determination of absolute stereochemistry. Our aim was to develop an enantioselective and flexible method to synthesize several members of the eusiderin family and their analogues. This would allow for the first determination of the absolute stereochemistry of eusiderins. Our approach is summarized in the retrosynthesis shown in Figure 3.

As stated, one of the main points of variation within the eusiderin family is the side chain; thus, it was thought that if this was introduced last, it would provide basis for the synthesis of a large number of natural products and analogues from the same common bromide. The open chain diol **6** can be cyclized through an acid-catalyzed reaction to form both *trans* and *cis* isomers of the 1,4-benzodioxane moiety. This open chain compound could be formed through the addition of an aryl organometallic species to a chiral aldehyde, itself formed from the reduction of the associated ester **7**. The substitution on the appended aromatic ring is a point of difference within the eusiderin family, so it is thought that the addition of a variety of organometallic reagents would facilitate the diversity and allow for ester **7** and its associated aldehyde to be a common starting material for all eusiderins. This ester **7** could be synthesized by the Mitsunobu reaction between phenol **8** and (*S*)-ethyl lactate **9**.

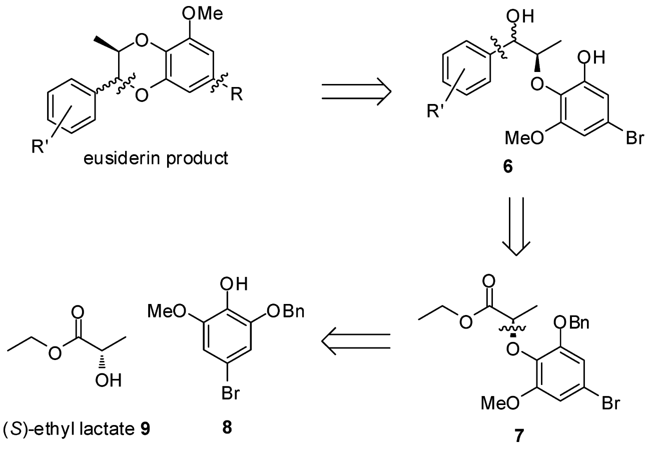
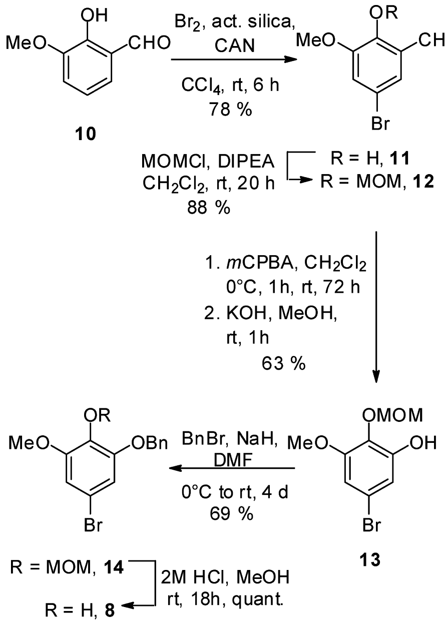


Figure 3. Retrosynthetic analysis of eusiderins.

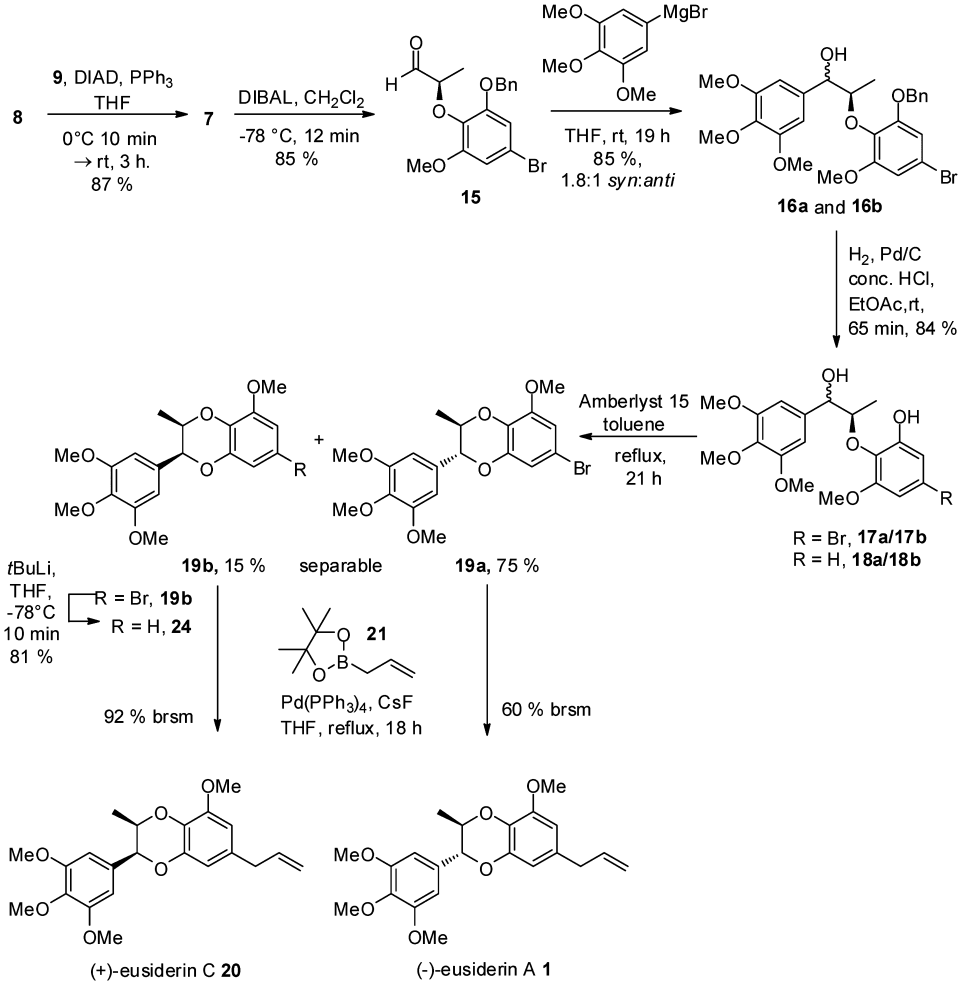
■ RESULTS AND DISCUSSION

We therefore began with the synthesis of phenol **8**, which contains the appropriate substitution around the aromatic ring that would form the aryl component of the 1,4-benzodioxane skeleton. *o*-Vanillin **10** was selectively brominated[25] to give the desired bromide **11** in a 78% yield (Scheme 1). The free phenol was then protected as a MOM ether **12**, in an 88% yield, which then allowed for selective manipulation of the aldehyde group.

Scheme 1. Synthesis of Phenol 8



Scheme 2. Synthesis of (−)-Eusiderin A 1 and (+)-Eusiderin C 20



Aldehyde **12** underwent a Baeyer−Villiger oxidation to give phenol **13** in a 63% yield. Phenol **13** was thereafter benzyl protected in a 69% yield, and the MOM ether in the resulting compound **14** removed with acid to provide phenol **8** in quantitative yield.

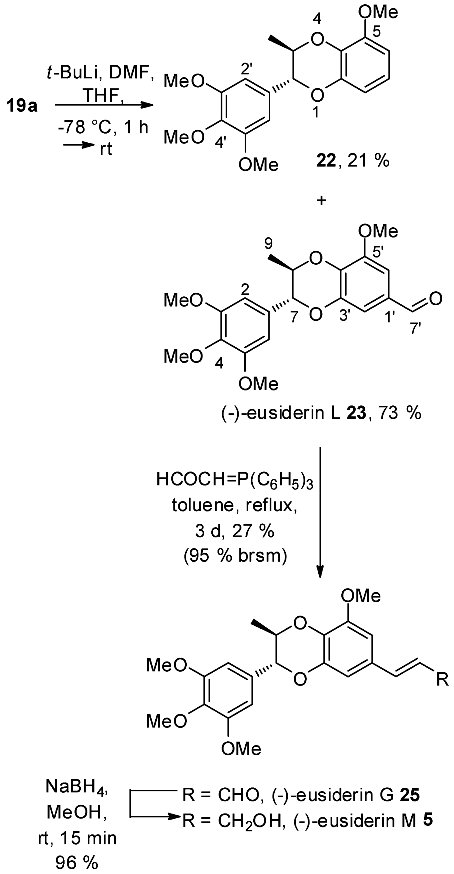
The next step was the Mitsunobu reaction between phenol **8** and (*S*)-ethyl lactate **9** which installs the first of two chiral centers in the eventual 1,4-benzodioxane. Using DIAD and THF as the solvent, the reaction gave the desired ether **7** in 87% yield (Scheme 2). Direct reduction of ester **7** to aldehyde **15** was achieved using DIBAL at −78 °C giving **15** in a good 85% yield, with no over-reduction seen.

With aldehyde **15** in hand, the next step was the addition of an aromatic organometallic reagent. In the eusiderins, the most common substitution pattern on this aromatic ring is 3,4,5-trimethoxy, so this was our initial target. Thus 3,4,5-trimethoxyphenylmagnesium bromide was added to aldehyde **15** to give alcohols **16a** and **16b** as 1.8:1 mixture of *syn* to *anti* diastereomers in 85% overall yield. This ratio can be explained through the adoption of the Cram chelate model, which predicts that the *syn* product is favored—a rationalization that is well supported in literature,[26] particularly by Chen et al.,[27] who were able to confirm through stop-flow NMR kinetic studies that high *syn* to *anti* stereoselectivity is associated with strong chelation, authenticating the 1959 postulate by Cram and Kopecky.[28] These two diastereomers were poorly separable and therefore reacted on as a mixture. The stereochemistry at C-1 is not important as during the cyclization step, isomerization occurs at this carbon.

The next step was the removal of the phenolic benzyl group via hydrogenation without the hydrogenolysis of the aromatic bromide.[29] A number of conditions were trialled,[30] giving a mixture of the alcohols **17a/b** along with the corresponding debrominated compounds **18a/b**. Ultimately using ethyl acetate, with the addition of concentrated HCl[31,32] gave a mixture of inseparable diols **17a** and **17b** in 84% yield. Refluxing the mixture of diols **17a/b** in toluene with Amberlyst 15 overnight[16] gave a separable 5:1 mixture of the *trans* **19a** and *cis* **19b** 1,4-benzodioxanes in 90% overall yield. Installation of the allylic side chain was achieved by reaction of *trans* bromide **19a** with boronate ester **21** giving (−)-eusiderin A **1** in a 60% yield based on returned starting material. If the reaction was left for longer than 24 h, debrominated product **22** was isolated, thus the reactions were stopped after less than 24 h and starting material was recovered and reacted again. Similarly reaction of *cis* bromide **19b**, under the same conditions, gave (+)-eusiderin C **20** in a 92% yield based on returned starting material. The NMR data and optical rotation, $[\alpha]_D = -22.9$ (c 0.83, MeOH), of the synthetic (−)-eusiderin A **1** matched the reported literature value, $[\alpha]_D = -25.4$ (c 1.80, MeOH).[18,19,33] No optical rotation for eusiderin C **20** has been reported, but the NMR data of the synthetic (+)-eusiderin C **20** matched the literature values.[19]

The next target was eusiderin L **23**, which has a formyl group side chain at C-7 (please note that upon addition of a side chain naming of the compounds changes to IUPAC lignan format). To introduce this group, the *trans* bromide **19a** was lithiated followed by the addition of dry DMF (Scheme 3). This procedure gave (−)-eusiderin L **23** in 73% yield, as well as **22** in 21% yield. No optical rotation of (−)-eusiderin L **23** has been reported, but the ^1H NMR data of the synthetic (−)-eusiderin L **23** matched the literature.[19] For use in the ECD study of these compounds (see below), the *cis* debromo analogue **24** was prepared at this time by the lithiation of *cis* bromide **19b**, in an 81% yield (Scheme 2). Wittig reaction of (−)-eusiderin L **23** gave (−)-eusiderin G **25** in 27% yield, which was 95% based on returned starting material (Scheme 3). No optical rotation of eusiderin G **25** has been reported, but the ^1H NMR data of the synthetic (−)-eusiderin G **25** matched literature values.[33] Reduction of the aldehyde in (−)-eusiderin G **25** gave (−)-eusiderin M **5** in 96% yield. Again, no optical rotation of (−)-eusiderin M **5** has been reported; however, the ^1H NMR data of the synthetic (−)-eusiderin M **5** matched the literature.[19]

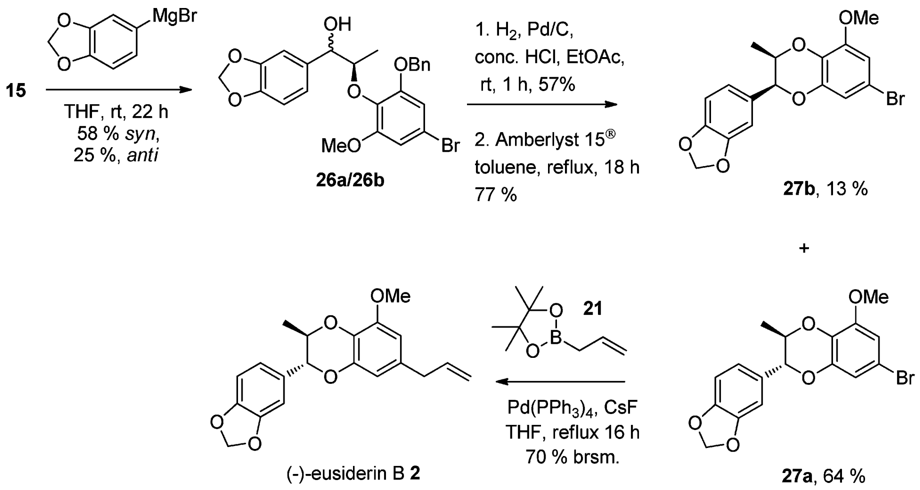
Scheme 3. Synthesis of (−)-Eusiderin L 23, (−)-Eusiderin G 25 and (−)-Eusiderin M 5

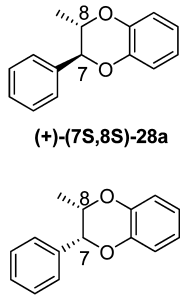


To demonstrate the flexibility not only in the scope of side chains that can be afforded from this method but also in the substitution on the appended ring, we then decided to synthesize eusiderin B **2**. Thus, 3,4-methylenedioxyphenylmagnesium bromide was added to aldehyde **15** (Scheme 4). The addition gave *syn* **26a** and *anti* **26b** alcohols, in a 2.3:1 ratio, in an 83% overall yield. Hydrogenation-deprotection followed by cyclization gave a 5:1 separable mixture of *trans* **27a** to *cis* **27b** products in 44% yield over 2 steps. Suzuki reaction of **27a**, with boronate ester **21**, gave (−)-eusiderin B **2** in 70% yield, based on returned starting material. The NMR data of the synthetic (−)-eusiderin B **2** matched reported literature values, however no optical rotation for eusiderin B **2** was reported.[34]

Determination of Absolute Stereochemistry. The relative stereochemistry of these 1,4-benzodioxanes can be easily determined by the 2-H and 3-H coupling constant—the *trans* isomer has a ∼8 Hz coupling constant, while the coupling constant for the *cis* isomer is ∼2 Hz.[16] Analysis of the ^1H NMR data of the synthesized 1,4-benzodioxanes show that a clear distinction between isomers can be made. The assignment of absolute stereochemistry is much more difficult. An ECD study by Arnoldi et al.[16] has been the basis for the assignment of the absolute stereochemistry of the eusiderin family. The ECD spectra of model 1,4-benzodioxanes (+)-(7*S*,8*S*)-**28a** and (−)-(7*R*,8*S*)-**28b** (for clarity the numbering is based on the lignan/eusiderin numbering pattern, Figure 4) were compared to that of the previously isolated eusiderin A **1** and eusiderin C **20** (Table 1). Eusiderin A **1** from *Virola pavonis* was thus assigned the (7*R*,8*R*) configuration and natural eusiderin C **20** a (7*R*,8*S*) configuration. Later, Da Silva et al.[19] isolated a sample of eusiderin C **20** from *Licaria chrysophylla* which

Scheme 4. Synthesis of (−)-Eusiderin B 2





(+)-(7S,8S)-28a

(-)-(7R,8S)-28b

Figure 4. Chiral 1,4-benzodioxanes **28a/b** prepared by Arnoldi et al.

Table 1. Configuration and ECD Comparison for Selected Natural and Synthetic Eusiderins

compound	sign of peak at approximately 240 nm	C-7 configuration	C-8 configuration
synthetic (−)-eusiderin A **1**	negative	R	R
eusiderin A **1** ex. *Virola pavonis*[16]	negative	R	R
synthetic (+)-eusiderin C **20**	negative	S	R
eusiderin C **20** ex. *Licaria chyrsophylla*[19]	negative	S	R
eusiderin C **20** ex. *Virola pavonis*[16]	positive	R	S
synthetic (−)-eusiderin B **2**	negative	R	R
trans 1,4-benzodioxane **28a**[16]	positive	S	S
cis 1,4-benzodioxane **28b**[16]	positive	R	S

incidentally had the opposite ECD spectra to that of the sample from *Virola pavonis*, indicating that both enantiomers occur in nature.

Benzodioxanes (+)-(7*S*,8*S*)-28a and (−)-(7*R*,8*S*)-28b.

Benzodioxanes (+)-(7*S*,8*S*)-**28a** and (−)-(7*R*,8*S*)-**28b** are, however, simplified models of the eusiderins, having no oxygenated substituents around the core structure that are so prevalent in the eusiderin family. It has been shown in the past that models with different substitution patterns are not reliable as references in assigning the absolute stereochemistry through ECD studies.[20] Thus, to confirm without reservation, the absolute stereochemistry of eusiderin A **1**, to determine which enantiomer of eusiderin C **20** is found in each plant species, as well as for reference when eusiderins are isolated in the future, we decided to measure the ECD spectrum of each of the synthetic 1,4-benzodioxanes.

The ECD spectra of *trans* and *cis* isomers of the same 1,4-benzodioxane show a high degree of similarity, as displayed by the isomeric pairs **19a** and **19b**, **22** and **24**, and (-)-eusiderin A **1** and (+)-eusiderin C **20** (Figure 5). The constant among these compounds is the stereochemistry at C-8; this indicates that the ECD curves of these compounds can be useful in determining the stereochemistry at C-8 by looking at the sign of the major peak in the 260−230 nm region, with a negative peak resulting from the 8*R* configuration (Table 1). The *cis* compounds **19b**, **20** and **24** show absorptions that are slightly red-shifted with respect to their *trans* counterparts **19a**, **1** and **22** respectively. The absolute stereochemistry of synthetic (−)-eusiderin A **1**, which has 7*R*,8*R* configuration had a similar optical rotation to the isolated natural product ([*α*]$_D$ −22.9, synthetic vs [*α*]$_D$ −25.4, natural).[18] In addition, comparison of the ECD curve of synthetic (−)-eusiderin A **1** with that of the natural compound[16] show they are of the same 7*R*,8*R* configuration. The ECD curve of synthetic (+)-eusiderin C **20** was compared to the ECD data of the natural compounds isolated from *Virola pavonis*[16] and *Licaria chrysophylla*.[19] It was concluded that the enantiomer isolated from *Licaria chrysophylla* was of the same absolute configuration, 7*S*,8*R*, as the synthesized (+)-eusiderin C **20**, while the enantiomeric compound from *Virola pavonis* has 7*R*,8*S* stereochemistry.

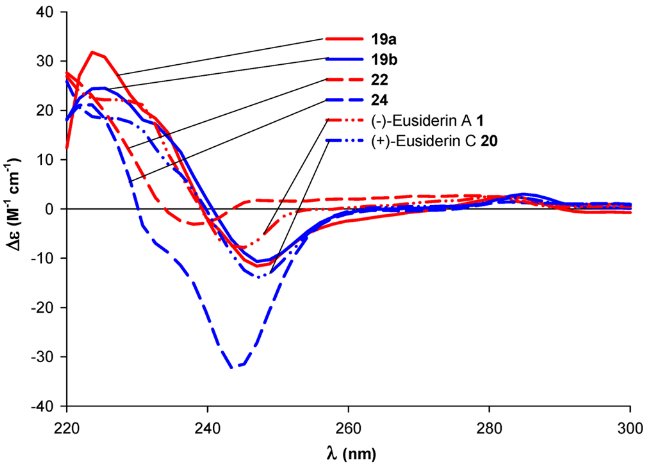


Figure 5. ECD spectra (MeOH) of **19a**, **19b**, **22**, **24**, (−)-eusiderin A **1** and (+)-eusiderin C **20**, *trans* isomers in red and *cis* isomers in blue.

All three 1,4-benzodioxanes with a 3,4-methylenedioxy group on the appended aromatic ring are similar in the 220−260 nm region to the 3,4,5-trimethoxy 1,4-benzodioxanes (Figure 6). They also have a large peak in the 300−270 nm region with both of the *trans* compounds **2** and **27a**, this peak is negative, while the *cis* compound **27b** has a positive peak in this region.

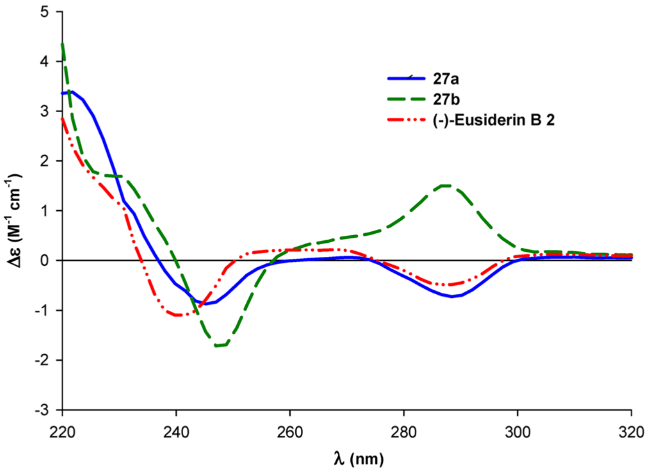


Figure 6. ECD spectra (MeOH) of **27a**, **27b** and (−)-eusiderin B **2**.

The presence and nature of the side chain had a varied effect on the shape of the ECD curve; with those having no side chain as for **22** and **24**, a bromine atom as for **19a** and **19b**, or an allyl group as for **1** and **20** all having similar ECD curves while the three eusiderins **5**, **23** and **25** that have additional conjugation on the side chain have different ECD spectra (Figure 7) when compared to each other and other eusiderins. As a result,

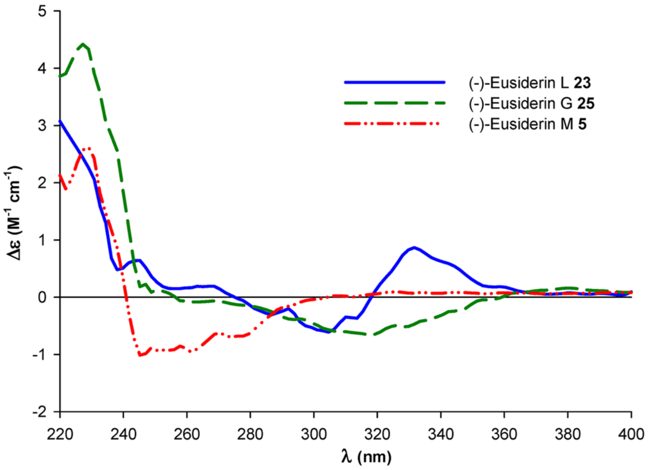


Figure 7. ECD spectra (MeOH) of (−)-eusiderin M **5**, (−)-eusiderin L **23** and (−)-eusiderin G **25**.

absolute stereochemical assignment based on ECD studies alone are unsuitable for these compounds. Despite this difficulty with using ECD spectra in assigning the absolute stereochemistry of these isolated natural products, no optical rotation readings were taken, with the exception of eusiderin A **1**,[18] and these eusiderins with additional conjugation as well as eusiderin B **2** were assigned their absolute stereochemistry based on their similarity to eusiderin A **1**, using neither ECD correlation or optical rotation.

Conclusions cannot be made about the absolute stereochemistry of naturally obtained eusiderins B **2**, G **25**, L **21** and M **5** as no chiroptical data has been reported for these natural products. We have shown that while comparison of the eusiderins containing conjugated side chains using ECD is not suitable, comparison of optical rotation values would be applicable for these compounds.[35] This work therefore provides a foundation for the assignment of absolute stereochemistry for eusiderins or similar 1,4-benzodioxanes that are isolated in the future. Relative stereochemistry can be assigned through analysis of the 2-H and 3-H coupling constant. Natural specimens of eusiderins A **1**, B **2**, C **20**, G **25**, L **21** and M **5** can be compared to the synthesized products through ECD or optical rotation. For other eusiderins, the ECD spectra should be analyzed—if the peak at ~240 nm is negative, the C-8 has an *R* configuration and if positive, an *S* configuration. For compounds with conjugated side chains the optical rotation should be measured—the measured optical rotations for the synthetic natural products do show a trend, and could provide an indication as to the absolute stereochemistry. All *trans* (7*R*,8*R*) products, eusiderins A **1**, B **2**, G **25**, L **23**, M **5** and analogues **19a** and **22** have a (−)-rotation, while all the *cis* (7*S*,8*R*) compounds **19b**, **20**, **24** and **27b** had a (+)-rotation. This observation in conjunction with the Arnoldi et al. readings indicates the sign of the optical rotation is dependent on the C-7 configuration; a positive optical rotation indicates a *S* configuration and a negative a *R* configuration.

CONCLUSION

In summary, the first asymmetric total synthesis of six eusiderins and a range of analogues has been achieved from aldehyde **15** using a method that facilitates the various points of difference within the eusiderin family. The ECD and optical rotation of isolated eusiderin A **1** were identical to that of the synthetic (−)-eusiderin A **1**, confirming the absolute stereochemistry of the natural product to be 7*R*,8*R*. Using ECD comparison eusiderin C **20**, from *Licaria chrysophylla*, was determined to have the same absolute configuration, 7*S*,8*R*, as the synthesized (+)-eusiderin C **20**. The spectroscopic data, in particular NMR, ECD and optical rotation, of the eusiderins and chiral 1,4-benzodioxanes reported here can assist in the determination of absolute stereochemistry in future isolated natural compounds of this type.

EXPERIMENTAL SECTION

All reactions were carried out under a nitrogen atmosphere in dry, freshly distilled solvents unless otherwise noted. All optical rotation measurements were determined at 20 °C on the sodium D line (λ = 589 nm, 0.1 dm cell). Ultraviolet−visible and circular dichroism spectra were run as methanol solutions. All NMR spectra were recorded on a 400 MHz spectrometer. Chemical shifts are reported relative to the solvent peak of chloroform (δ 7.26 for ^{1}H and δ 77.0 for ^{13}C). ^{1}H NMR data is reported as position (δ), relative integral, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak; qd, quartet of doublets), coupling constant (*J*, Hz), and the assignment of the atom. ^{13}C NMR data are reported as position (δ) and assignment of the atom. NMR assignments were performed using HSQC and HMBC experiments. The numbering of the natural products (**1**, **2**, **5**, **20**, **23**, **25**) is done in accordance with lignan nomenclature, which numbers each lignan fragment from C1 to C9.[36] High-resolution mass spectroscopy (HRMS) was carried out by either chemical ionization (CI) or electrospray ionization (ESI) on a MicroTOF-Q mass spectrometer. Unless noted, chemical reagents were used as purchased.

5-Bromo-2-hydroxy-3-methoxybenzaldehyde, 11. To a solution of *o*-vanillin **10** (8.0 g, 0.053 mol) in CCl_4 (160 mL) was added activated silica[25] (19.0 g), bromine (2.70 mL, 0.053 mol) and CAN (0.160 g, 0.292 mmol). The mixture was stirred at room temperature under an atmosphere of nitrogen for 6 h. The solids were then removed by filtration through a plug of silica and washed three times with CH_2Cl_2. The combined filtrate and washings were washed with aq. thiosulfate solution (100 mL), dried ($MgSO_4$) and the solvent was removed *in vacuo*. The solid was dissolved in 60% aqueous EtOH (500 mL). After heating, the remaining solid was removed by filtration while the solution was still hot. The filtrate was allowed to cool and then filtered to give a yellow solid as the title product **11** (9.52 g, 78%). R_f (4:1 *n*-hexanes, ethyl acetate) 0.47; mp 119−122 °C [lit.[25] 122−123 °C]; δ_H (400 MHz; $CDCl_3$; Me_4Si) 3.92 (3H, s, OMe), 7.18 (1H, d, *J* = 2.4 Hz, H-4), 7.31 (1H, d, *J* = 2.4 Hz, H-6), 9.86 (1H, s, CHO) and 10.99 (1H, s, OH); δ_C (100 MHz; $CDCl_3$) 56.5 (OMe), 111.0 (C-5), 120.7 (C-6), 121.3 (C-1), 126.1 (C-4), 149.2 (C-2), 150.9 (C-3) and 195.3 (CHO). The ^{1}HNMR was in agreement with literature values.[37]

5-Bromo-3-methoxy-2-(methoxymethoxy)benzaldehyde, 12. To phenol **11** (5.56 g, 0.024 mol) in CH_2Cl_2 (250 mL) at room temperature, under an atmosphere of nitrogen, was added DIPEA (17.19 mL, 0.096 mol) followed by MOMCl (6.0 mL, 0.060 mol) and the mixture was stirred at room temperature for 20 h. Sat. aq. NH_4Cl (80 mL) was added and the organic layer separated. The aqueous layer was further extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (2:1 *n*-hexanes, ethyl acetate) to yield the title product **12** (5.83 g, 88%) as white solid. R_f (4:1 *n*-hexanes, ethyl acetate) 0.52; mp 63−64 °C; δ_H (400 MHz; $CDCl_3$; Me_4Si) 3.55 (3H, s, OCH_2OCH_3), 3.89 (3H, s, OMe), 5.21 (2H, s, OCH_2O), 7.23 (1H, d, *J* = 1.2 Hz, H-4), 7.53 (1H, d, *J* = 1.2 Hz, H-6) and 10.38 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 56.3 (OMe), 57.9 (OCH_2OCH_3), 99.3 (OCH_2OCH_3), 117.2 (C-5), 120.6 (C-4), 121.6 (C-6), 131.0 (C-1), 148.4 (C-2), 153.2 (C-3) and 188.8 (CHO). The ^{1}HNMR was in agreement with literature values.[38]

5-Bromo-3-methoxy-2-(methoxymethoxy)phenol, 13. To a solution of aldehyde **12** (5.83 g, 0.021 mol) in CH_2Cl_2 (150 mL) under an atmosphere of nitrogen at 0 °C, was added *m*CPBA (10.97 g, 0.064 mol). The reaction was stirred at 0 °C for 1 h and then left to warm to room temperature and stirred for 72 h. To the resulting suspension was added sat. aq. $Na_2S_2O_3$ (100 mL) and the mixture extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with sat. aq. Na_2CO_3 (75 mL), sat. aq. NH_4Cl (75 mL) and brine (75 mL). The organic layer was then dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was suspended in a solution of KOH (8.0 g) in methanol (200 mL) and stirred at room temperature for 1 h. The resulting solution was added to 2 M HCl (80 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with sat. aq. Na_2CO_3 (75 mL) and brine (75 mL), dried (Na_2SO_4) and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (2:1 *n*-hexanes, ethyl acetate) to yield the title product **13** (3.53 g, 63%) as an off-white solid. R_f (4:1 *n*-hexanes, ethyl acetate) 0.35; mp 150−152 °C; ν_{max}(film)/cm^{-1} 3385 (OH), 2939 and 2842 (CH), 1688 (C=O), 1591 and 1494 (C=C), 1326, 1197, 1162, 1108, 948 and 850; δ_H (400 MHz; $CDCl_3$; Me_4Si) 3.58 (3H, s, OCH_2OCH_3), 3.82 (3H, s, OMe), 5.07 (2H, s, OCH_2O), 6.60 (1H, d, *J* = 2.4 Hz, H-4), 6.79 (1H, d, *J* = 2.4 Hz, H-6) and 6.84 (1H, s, OH); δ_C (100 MHz; $CDCl_3$) 56.1 (OMe), 57.6 (OCH_2OCH_3), 99.6 (OCH_2OCH_3), 107.5 (C-4), 112.6 (C-6), 117.2 (C-5), 133.3 (C-2), 150.5 (C-1) and 152.7 (C-3); *m*/*z* (ESI+): 287 ($^{81}BrMNa^+$, 95%), 285 ($^{79}BrMNa^+$, 100), 277 (10) and 266 (10); HRMS (ESI+) Found (MNa^+): 286.9708 $C_9H_{11}{}^{81}BrNaO_4$ requires 286.9713. Found (MNa^+): 284.9728 $C_9H_{11}{}^{79}BrNaO_4$ requires 284.9733.

1-(Benzyloxy)-5-bromo-3-methoxy-2-(methoxymethoxy)-benzene, 14. To a stirred solution of NaH (60% w/w dispersion in mineral oil, 0.778 g, 0.016 mol) washed with pentane in DMF (60 mL) under an atmosphere of nitrogen at 0 °C was added a solution of phenol **13** (3.53 g, 0.013 mol) in DMF (40 mL). The resulting mixture was stirred for 20 min. Benzyl bromide (1.59 mL, 0.013 mol) was then added and the mixture was allowed to warm to room temperature then stirred for 4 days. The reaction mixture was treated with sat. aq. NH_4Cl (75 mL) and extracted with diethyl ether (4 × 75 mL). The combined organic extracts were collected, dried ($MgSO_4$), and concentrated *in vacuo*, and the residue purified with flash chromatography (9:1 *n*-hexanes, ethyl acetate) to give the title product **14** (3.27 g, 69%) as a colorless oil. R_f (4:1 *n*-hexanes, ethyl acetate) 0.51; ν_{max}(film)/cm^{-1} 2937 (CH), 1590 and 1492 (C=C), 1416, 1230, 1156, 1118, 1079, 962, 738 and 698; δ_H (400 MHz; $CDCl_3$; Me_4Si) 3.50 (3H, s, OCH_2OCH_3), 3.77 (3H, s, OMe), 5.00 (2H, s, OCH_2O), 5.08 (2H, s, OCH_2Ar), 6.70 (1H, d, *J* = 2.4 Hz, H-6), 6.76 (1H, d, *J* = 2.4 Hz, H-4) and 7.29−7.35 (5H, m, Ar−H); δ_C (100 MHz; $CDCl_3$) 56.2 (OMe), 57.2 (OCH_2OCH_3), 71.2 (OCH_2Ph), 98.2 (OCH_2OCH_3), 109.2 (C-6), 110.5 (C-4), 116.4 (C-5), 127.5 (Ar−CH), 128.1 (Ar−CH), 128.6 (Ar−CH), 134.3 (C-2), 136.2 (Ar−C), 153.1 (C-1) and 154.1 (C-3); *m*/*z* (ESI+): 377 ($^{81}BrMNa^+$, 100%), 375 ($^{79}BrMNa^+$, 99), 351 (20), 353 (20) and 229 (85); HRMS (ESI+) Found (MNa^+): 377.0178 $C_{16}H_{17}{}^{81}BrNaO_4$ requires 377.0183. Found (MNa^+): 375.0197 $C_{16}H_{17}{}^{79}BrNaO_4$ requires 375.0202.

2-(Benzyloxy)-4-bromo-6-methoxyphenol, 8. To a solution of ether **14** (1.70 g, 4.81 mmol) in MeOH (150 mL) was added 2 M HCl (14 mL) and the resultant mixture stirred at room temperature for 18 h. One M NaOH was added until the solution was pH 5 and then the solution was extracted with ethyl acetate (3 × 80 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (3:1 *n*-hexanes, ethyl acetate) to give the title product **8** (1.50 g, quant.) as an orange solid. R_f (4:1 *n*-hexanes, ethyl acetate) 0.38; mp 73−76 °C; ν_{max}(film)/cm^{-1} 3511 (OH), 2937 (CH), 1607 and 1502 (C=C), 1448, 1421, 1204, 1097, 772 and 697; δ_H (400 MHz; $CDCl_3$; Me_4Si) 3.86 (3H, s, OMe), 5.08 (2H, s, OCH_2Ph), 5.52 (1H, br s, OH), 6.72 (1H, d, *J* = 2.4 Hz, H-6), 6.78 (1H, d, *J* = 2.4 Hz, H-4) and 7.34−7.43 (5H, m, Ar−H); δ_C (100 MHz; $CDCl_3$) 56.4 (OMe), 71.6 (OCH_2Ph), 108.9 (C-6), 110.1 (C-4), 110.9 (C-5), 127.7 (Ar−CH), 128.4 (Ar−CH), 128.7 (Ar−CH), 134.6 (C-2), 136.0 (Ar−C), 146.7 (C-1) and 147.8 (C-3); *m*/*z* (ESI+): 333 ($^{81}BrMNa^+$, 95%), 331 ($^{79}BrMNa^+$, 100), 311 (22) and 309 (22); HRMS (ESI+) Found (MNa^+): 332.9916 $C_{14}H_{13}{}^{81}BrNaO_3$ requires 332.9920. Found (MNa^+): 330.0038 $C_{14}H_{13}{}^{79}BrNaO_3$ requires 330.0040.

(2*R*)-Ethyl 2-(2′-(benzyloxy)-4′-bromo-6′-methoxyphenoxy)-propanoate, 7. To phenol **8** (2.34 g, 7.57 mmol) and (*S*)-ethyl lactate **9** (1.56 g, 13.0 mmol) in THF (150 mL) under an atmosphere of nitrogen, was added PPh_3 (3.47 g, 13.0 mmol). The solution was cooled to 0 °C and DIAD (2.61 mL, 13.0 mmol) was added slowly. The reaction mixture was kept at 0 °C for 10 min and then allowed to warm to room temperature. After stirring at room temperature for 3 h, the mixture was concentrated *in vacuo*. The crude product was purified by flash chromatography (9:1 *n*-hexanes, ethyl acetate) to yield the title product **7** (2.68 g, 87%) as a colorless oil. R_f (4:1 *n*-hexanes, ethyl acetate) 0.52; $[\alpha]_D$ +30.6 (*c* 1.08, $CHCl_3$); ν_{max}(film)/cm^{-1} 2983 and 2937 (CH), 1733 (C=O), 1589 and 1490 (C=C), 1416, 1197, 1117, 735 and 697; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.20 (3H, t, *J* = 7.2 Hz, CH_2CH_3), 1.50 (3H, d, *J* = 6.8 Hz, H-3), 3.81 (3H, s, OMe), 4.10 (2H, q, *J* = 7.2 Hz, CH_2CH_3), 4.61 (1H, q, *J* = 6.8 Hz, H-2), 5.05 (2H, s, OCH_2Ar), 6.71 (1H, d, *J* = 2.0 Hz, H-5′), 6.76 (1H, d, *J* = 2.0 Hz, H-3′) and 7.32−7.41 (5H, m, Ar−H); δ_C (100 MHz; $CDCl_3$) 14.1 (OCH_2CH_3), 18.4 (C-3), 56.3 (OMe), 60.8 (OCH_2CH_3), 71.4 (OCH_2Ar), 77.5 (C-2), 109.4 (C-5′), 110.9 (C-3′), 116.2 (C-4′), 127.4 (C-2″), 128.0 (C-4″), 128.5 (C-3″), 136.0 (C-1′), 136.4 (C-1″), 152.8 (C-2′), 154.0 (C-6′) and 171.9 (C-1); *m*/*z* (ESI+): 433 ($^{81}BrMNa^+$, 98%), 431 ($^{79}MNa^+$, 100), 411 ($^{81}BrMH^+$, 15), 409 ($^{79}BrMH^+$, 15) and 91 (7); HRMS (ESI+) Found (MNa^+): 433.0462 $C_{19}H_{21}{}^{81}BrNaO_5$ requires 433.0445. Found (MNa^+): 431.0481 $C_{19}H_{21}{}^{79}BrNaO_5$ requires 431.0465.

(2*R*)-2-(2′-(Benzyloxy)-4′-bromo-6′-methoxyphenoxy)-propanal, 15. To a solution of ester **7** (2.67 g, 6.55 mmol) in CH_2Cl_2 (150 mL), under an atmosphere of nitrogen at −78 °C, was added DIBAL (1 M in *n*-hexanes, 9.82 mL, 9.82 mmol) and the mixture stirred for 12 min. The reaction was quenched with 2 M HCl (80 mL) then extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (4:1 *n*-hexanes, ethyl acetate) to yield the title product **15** (2.02 g, 85%) as a white solid. R_f (2:1 *n*-hexanes, ethyl acetate) 0.60; $[\alpha]_D$ +28.5 (*c* 1.054, $CHCl_3$); mp: 92−95 °C; ν_{max}(film)/cm^{-1} 2936 (CH), 1731 (C=O), 1590 and 1490 (C=C), 1415, 1221, 1114, 812 and 698; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.38 (3H, d, *J* = 7.2 Hz, H-3), 3.82 (3H, s, OMe), 4.27 (1H, qd, *J* = 2.0, 7.2 Hz, H-2), 5.06 (2H, s, OCH_2Ph), 6.73 (1H, d, *J* = 2.4 Hz, H-5′), 6.79 (1H, d, *J* = 2.4 Hz, H-3′), 7.34−7.40 (5H, m, Ar−H) and 9.86 (1H, d, *J* = 2.0 Hz, CHO); δ_C (100 MHz; $CDCl_3$) 16.0 (C-3), 56.2 (OMe), 71.3 (OCH_2Ph), 83.3 (C-2), 109.1 (C-5′), 110.5 (C-3′), 116.7 (C-4′), 127.4 (Ar−CH), 128.2 (Ar−CH), 128.6 (Ar−CH), 135.7 (C-1′), 136.0 (Ar−C), 152.8 (C-2′), 153.7 (C-6′) and 203.4 (C-1). *m*/*z* (ESI+): 367 ($^{81}BrMH^+$, 100%), 365 ($^{79}MH^+$, 95), 300 (30) and 101 (50); HRMS (ESI+) Found (MH^+): 367.0357 $C_{17}H_{18}{}^{81}BrO_4$ requires 367.0363. Found (MH^+): 365.0374 $C_{17}H_{18}{}^{79}BrO_4$ requires 365.0383.

(1*R*,2*R*)-2-(2′-(Benzyloxy)-4′-bromo-6′-methoxyphenoxy)-1-(3″,4″,5″-trimethoxyphenyl)propan-1-ol, 16a and (1*S*,2*R*)-2-(2′-(Benzyloxy)-4′-bromo-6′-methoxyphenoxy)-1-(3″,4″,5″-trimethoxyphenyl)propan-1-ol, 16b. To a solution of aldehyde **15** (0.390 g, 1.07 mmol) in THF (16 mL) under an atmosphere of nitrogen, at room temperature was added 3,4,5-trimethoxyphenylmagnesium bromide (0.5 M in THF, 6.41 mL, 3.21 mmol). After stirring at room temperature for 19 h, sat. aq. NH_4Cl (10 mL) was added and the aqueous mixture extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (3:1 *n*-hexanes, ethyl acetate) to yield the title products **16a**, **16b** in a 1.8:1 ratio as a poorly separable mixture of diastereomers (0.481 g, 85%) as an orange oil. **16a**; R_f (2:1 *n*-hexanes, ethyl acetate) 0.37; ν_{max}(film)/cm^{-1} 3519 (OH), 2938 (CH), 1590 and 1493 (C=C), 1417, 1231, 1126, 1006, 735 and 699; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.10 (3H, d, *J* = 6.4 Hz, H-3), 3.75 (1H, s, OH), 3.81 (9H, s, 3 x OMe), 3.88 (3H, s, OMe), 4.33 (1H, qd, *J* = 2.8, 6.4 Hz, H-2), 4.80 (1H, d, *J* = 2.8 Hz, H-1), 5.10 (2H, s, OCH_2Ph), 6.50 (2H, s, H-2″ and H-6″), 6.79 (1H, d, *J* = 2.0 Hz, H-5′), 6.86 (1H, d, *J*

= 2.0 Hz, H-3′) and 7.33−7.40 (5H, m, Ar−H); δ_C (100 MHz; CDCl$_3$) 12.7 (C-3), 56.1 (OMe), 56.4 (OMe), 60.8 (OMe), 71.5 (OCH$_2$Ph), 73.2 (C-1), 82.7 (C-2), 103.0 (C-2″ and C-6″), 109.3 (C-5′), 110.9 (C-3′), 116.4 (C-4′), 127.4 (Ar−CH), 128.4 (Ar−CH), 128.7 (Ar−CH), 134.8 (C-1′), 135.3 (Ar−C), 136.0 (C-1″), 136.9 (C-4″), 153.1 (C-3″ and C-5″), 153.4 (C-2′) and 154.3 (C-6′). **16b**; R_f (2:1 *n*-hexanes, ethyl acetate) 0.32; δ_H (400 MHz; CDCl$_3$; Me$_4$Si) 1.12 (3H, d, *J* = 6.4 Hz, H-3), 3.62 (1H, s, OH), 3.78 (3H, s, OMe), 3.81 (9H, s, 3 x OMe), 4.07−4.10 (1H, m, H-2), 4.55 (1H, d, *J* = 7.6 Hz, H-1), 5.09 (2H, s, OC*H*$_2$Ph), 6.54 (2H, s, H-2″ and H-6″), 6.76 (1H, d, *J* = 2.4 Hz, H-5′), 6.83 (1H, d, *J* = 2.4 Hz, H-3′) and 7.33−7.39 (5H, m, Ar−H); δ_C (100 MHz; CDCl$_3$) 17.5 (C-3), 56.0 (OMe), 56.1 (OMe), 60.8 (OMe), 71.6 (OCH$_2$Ph), 79.1 (C-1), 85.7 (C-2), 104.3 (C-2″ and C-6″), 109.4 (C-5′), 110.7 (C-3′), 116.1 (C-4′), 127.7 (Ar−CH), 128.4 (Ar−CH), 128.7 (Ar−CH), 135.8 (C-1′), 136.1 (Ar−C), 136.4 (C-1″), 137.6 (C-4″), 153.1 (C-3″ and C-5″), 153.6 (C-2′) and 153.8 (C-6′); *m/z* (ESI+): 557 (^{81}BrMNa$^+$, 100%), 555 (^{79}MNa$^+$, 95), 360 (33), 227 (15) and 159 (5); HRMS (ESI+) Found (MNa$^+$): 557.0954 $C_{26}H_{29}{}^{81}BrNaO_7$ requires 557.0970. Found (MNa$^+$): 555.0971 $C_{26}H_{29}{}^{79}BrNaO_7$ requires 555.0989.

(1*R*,2*R*)-2-(4′-Bromo-2′-hydroxy-6′-methoxyphenoxy)-1-(3″,4″,5″-trimethoxyphenyl)propan-1-ol, 17a and (1*S*,2*R*)-2-(4′-Bromo-2′-hydroxy-6′-methoxyphenoxy)-1-(3″,4″,5″-trimethoxyphenyl)propan-1-ol, 17b. To a 1.8:1 mixture of benzyl ethers **16a/b** (0.870 g, 1.63 mmol) in ethyl acetate (60 mL) was added 37% HCl (1.8 mL) and 10% Pd/C (0.131 g) and the mixture stirred under an atmosphere of hydrogen for 65 min. The mixture was filtered through Celite and the filtrate washed with sat. aq. NaHCO$_3$ (2 × 50 mL) and water (50 mL). The aqueous washings were further extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were dried (MgSO$_4$) and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (4:1 *n*-hexanes, ethyl acetate) to yield the title products **17a**, **17b** (0.610 g, 84%) as an inseparable 1.8:1 mixture, as a viscous yellow oil. **17a**: R_f (2:1 *n*-hexanes, ethyl acetate) 0.38; ν_{max}(film)/cm^{-1} 3391 (OH), 2939 (CH), 1589 and 1493 (C=C), 1455, 1222, 1126, 1103, 908 and 727; δ_H (400 MHz; CDCl$_3$; Me$_4$Si) 1.16 (3H, d, *J* = 6.4 Hz, H-3), 3.05 (1H, br s, 1-OH), 3.82 (3H, s, OMe), 3.83 (3H, s, OMe), 3.84 (6H, s, 2 x OMe), 4.31 (1H, qd, *J* = 3.2, 6.4 Hz, H-2), 4.83 (1H, d, *J* = 3.2 Hz, H-1), 6.55 (2H, s, H-2″ and H-6″), 6.61 (1H, d, *J* = 2.4 Hz, H-5′), 6.77 (1H, d, *J* = 2.4 Hz, H-3′) and 7.46 (1H, br s, Ar−O*H*); δ_C (100 MHz; CDCl$_3$) 14.0 (C-3), 56.1 (OMe), 56.2 (OMe), 60.8 (OMe), 75.3 (C-1), 82.0 (C-2), 103.6 (C-2″ and C-6″), 107.5 (C-5′), 112.5 (C-3′), 116.8 (C-4′), 132.6 (C-1′), 135.2 (C-1″), 137.5 (C-4″), 152.0 (C-2′), 153.2 (C-3″ and C-5″) and 153.7 (C-6′). **17b**: R_f (2:1 *n*-hexanes, ethyl acetate) 0.33; δ_H (400 MHz; CDCl$_3$; Me$_4$Si) 1.15 (3H, d, *J* = 6.4 Hz, H-3), 3.82 (6H, s, 2 × OMe), 3.83 (6H, s, 2 × OMe), 3.91−3.94 (1H, m, H-2), 4.65 (1H, d, *J* = 8.4 Hz, H-1), 6.51 (2H, s, H-2″ and H-6″), 6.58 (1H, d, *J* = 2.4 Hz, H-5′), 6.77 (1H, d, *J* = 2.4 Hz, H-3′) and 8.64 (1H, br s, Ar−O*H*); δ_C (100 MHz; CDCl$_3$) 17.7 (C-3), 56.1 (OMe), 60.8 (OMe), 79.5 (C-1), 85.6 (C-2), 103.9 (C-2″ and C-6″), 107.1 (C-5′), 113.0 (C-3′), 116.9 (C-4′), 134.5 (C-1′), 135.6 (C-1″), 138.0 (C-4″), 151.8 (C-2′), 153.4 (C-3″ and C-5″) and 153.7 (C-6); *m/z* (ESI+): 467 (^{81}BrMNa$^+$, 100%), 465 (^{79}MNa$^+$, 95), 359 (25) and 357 (25). HRMS (ESI+) Found (MNa$^+$): 467.0502 $C_{19}H_{23}{}^{81}BrNaO_7$ requires 467.0500. Found (MNa$^+$): 465.0522 $C_{19}H_{23}{}^{79}BrNaO_7$ requires 465.0519.

(2*R*,3*R*)-3-Methyl-2-(3′,4′,5′-trimethoxyphenyl)-7-bromo-5-methoxy-1,4-benzodioxane, 19a and (2*S*,3*R*)-3-Methyl-2-(3′,4′,5′-trimethoxyphenyl)-7-bromo-5-methoxy-1,4-benzodioxane, 19b. A mixture of diols **17a** and **17b** (0.560 g, 1.29 mmol) and Amberlyst 15 (0.080 g) in dry toluene (20 mL), under an atmosphere of nitrogen, was refluxed for 21 h. The solution was filtered and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (4:1 *n*-hexanes, ethyl acetate) to yield the title product **19a** (0.384 g, 75%) as a light brown crystalline solid. R_f (4:1 *n*-hexanes, ethyl acetate) 0.33; mp: 148−150 °C; $[\alpha]_D$ −12.9 (*c* 0.70, MeOH); ECD (MeOH; *c* 1.1 mg/10 mL) λ ($\Delta\varepsilon$) 224 (+3.8), 239 (0), 247 (−1.4), 273 (0), 283 (+0.3), 290 (0) nm; UV (MeOH) λ_{max} (log ε) 270 (0.48) nm; ν_{max}(film)/cm^{-1} 2938 (CH), 1596 and 1496 (C=C), 1463, 1354, 1222, 1149, 1126, 1107, 1006 and 728; δ_H (400 MHz; CDCl$_3$; Me$_4$Si) 1.26 (3H, d, *J* = 6.4 Hz, CH$_3$), 3.86 (3H, s, OMe), 3.88 (9H, s, 3 × OMe), 4.05−4.12 (1H, m, H-3), 4.55 (1H, d, *J* = 8.0 Hz, H-2), 6.56 (2H, s, H-2′, H-6′), 6.66 (1H, d, *J* = 1.6 Hz, H-6) and 6.79 (1H, d, *J* = 1.6 Hz, H-8); δ_C (100 MHz; CDCl$_3$) 17.2 (CH$_3$), 56.2 (OMe), 56.3 (OMe), 60.8 (OMe), 74.2 (C-3), 81.1 (C-2), 104.4 (C-2′ and C-6′), 107.9 (C-6), 112.1 (C-7), 113.0 (C-8), 131.9 (C-1′), 132.4 (C-4a), 138.6 (C-4′), 145.0 (C-8a), 149.2 (C-5) and 153.5 (C-3′ and C-5′); *m/z* (ESI+): 449 (^{81}BrMNa$^+$, 100%), 447 (^{79}MNa$^+$, 95), 408 (20) and 360 (80); HRMS (ESI+) Found (MNa$^+$): 449.0385 $C_{19}H_{21}{}^{81}BrNaO_6$ requires 449.0394. Found (MNa$^+$): 447.0405 $C_{19}H_{21}{}^{79}BrNaO_6$ requires 447.0414. In a separate fraction, the title product **19b** (0.079 g, 15%) was collected as a pale yellow oil. R_f (4:1 *n*-hexanes, ethyl acetate) 0.27; $[\alpha]_D$ + 50.8 (*c* 0.65, MeOH); ECD (MeOH; *c* 0.9 mg/10 mL) λ ($\Delta\varepsilon$) 225 (+3.6), 240 (0), 247 (−1.6), 266 (0), 285 (+0.4), 300 (0) nm; UV (MeOH) λ_{max} (log ε) 272 (0.35) nm; ν_{max}(film)/cm^{-1} 2939 (CH), 1592 and 1494 (C=C), 1463, 1418, 1209, 1124, 1006 and 732; δ_H (400 MHz; CDCl$_3$; Me$_4$Si) 1.13 (3H, d, *J* = 6.4 Hz, CH$_3$), 3.85 (3H, s, OMe), 3.87 (6H, s, 2 × OMe), 3.88 (3H, s, OMe), 4.59 (1H, qd, *J* = 2.4, 6.4 Hz, H-3), 5.11 (1H, d, *J* = 2.4 Hz, H-2), 6.59 (2H, s, H-2′, H-6′), 6.68 (1H, d, *J* = 2.4 Hz, H-6), 6.85 (1H, d, *J* = 2.0 Hz, H-8); δ_C (100 MHz; CDCl$_3$) 12.6 (CH$_3$), 56.2 (OMe), 56.4 (OMe), 60.9 (OMe), 73.3 (C-3), 77.2 (C-2), 103.1 (C-2′ and C-6′), 108.4 (C-6), 112.0 (C-7), 113.2 (C-8), 130.7 (C-4a), 131.8 (C-1′), 137.9 (C-4′), 144.1 (C-8a), 149.9 (C-5) and 153.5 (C-3′ and C-5′); *m/z* (ESI+): 427 (^{81}BrMH$^+$, 5%), 425 (^{79}MH$^+$, 5), and 360 (100); HRMS (ESI+) Found (MH$^+$): 427.0579 $C_{19}H_{22}{}^{81}BrO_6$ requires 427.0575. Found (MH$^+$): 425.0595 $C_{19}H_{22}{}^{79}BrO_6$ requires 425.0594.

(−)-Eusiderin A, 1. To a solution of bromide **19a** (21.2 mg, 0.050 mmol) in dry THF (1.5 mL), under an atmosphere of nitrogen, was added allyl boronic acid pinacol ester **21** (0.014 mL, 0.075 mmol), CsF (30.0 mg, 0.20 mmol) and Pd(PPh$_3$)$_4$ (0.3 mg, 0.003 mmol) and the mixture heated at reflux for 18 h. After cooling to room temperature ethyl acetate (2 mL) was added, followed by brine (2 mL). The layers were then separated and the aqueous layer further extracted with ethyl acetate (2 × 5 mL). The combined organic extracts were dried (MgSO$_4$) and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (4:1 *n*-hexanes, ethyl acetate) to yield the title product (−)-**1** (2.4 mg, 60% brsm.) as a colorless oil. Bromide **19a** (16.8 mg), was also recovered from this reaction. R_f (4:1 *n*-hexanes, ethyl acetate) 0.33; $[\alpha]_D$ −22.9 (*c* 0.83, MeOH); [lit.[18] $[\alpha]_D$ −25.4 (*c* 1.80, MeOH)]; ECD (MeOH; *c* 1.1 mg/10 mL) λ ($\Delta\varepsilon$) 220 (+2.8), 227 (+2.4), 239 (0), 245 (−0.8), 258 (0), 281 (+0.3) nm; UV (MeOH) λ_{max} (log ε) 272 (0.60) nm; ν_{max}(film)/cm^{-1} 2936 (CH), 1593 and 1506 (C=C), 1461, 1224, 1123, 1096, 1005, and 728; δ_H (400 MHz; CDCl$_3$; Me$_4$Si) 1.26 (3H, d, *J* = 6.4 Hz, H-9), 3.29 (2H, d, *J* = 6.8 Hz, H-7′), 3.86 (3H, s, OMe), 3.88 (6H, s, 2 × OMe), 3.89 (3H, s, OMe), 4.08−4.13 (1H, m, H-8), 4.55 (1H, d, *J* = 7.6 Hz, H-7), 5.04−5.13 (2H, m, H-9′), 5.90−6.00 (1H, m, H-8′), 6.38 (1H, d, *J* = 2.0 Hz, H-6′), 6.48 (1H, d, *J* = 2.0 Hz, H-2′), 6.58 (2H, s, H-2 and H-6); δ_C (100 MHz; CDCl$_3$) 17.3 (C-9), 40.0 (C-7′), 56.1 (OMe), 56.2 (OMe), 60.8 (OMe), 74.1 (C-8), 81.1 (C-7), 104.5 (C-2 and C-6), 104.6 (C-6′), 109.6 (C-2′), 115.8 (C-9′), 131.3 (C-4′), 132.4 (C-1), 132.5 (C-1′), 137.3 (C-8′), 138.5 (C-4), 144.3 (C-3′), 148.6 (C-5′) and 153.5 (C-3 and C-5); *m/z* (APCI+): 387 (MH$^+$, 75%), 338 (100), 271 (50), 208 (70) and 149 (50); HRMS (APCI+) Found (MH$^+$): 387.1794 $C_{22}H_{27}O_6$ requires 387.1802. All NMR data was in agreement with literature values.[19,33]

(+)-Eusiderin C, 20. To a solution of bromide **19b** (54.0 mg, 0.127 mmol) in dry THF (2 mL), under an atmosphere of nitrogen, was added allyl boronic acid pinacol ester **21** (0.036 mL, 0.190 mmol), CsF (77.0 mg, 0.507 mmol) and Pd(PPh$_3$)$_4$ (0.6 mg, 0.006 mmol) and the mixture heated at refluxed for 18 h. After cooling to room temperature ethyl acetate (2 mL) was added, followed by brine (2 mL). The layers were then separated and the aqueous layer further extracted with ethyl acetate (2 × 5 mL). The combined organic extracts were dried (MgSO$_4$) and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (4:1 *n*-hexanes, ethyl acetate) to yield the title product (+)-**20** (14.2 mg, 92% brsm.) as a colorless oil. Bromide **19b** (37 mg), was also recovered from this reaction. R_f (4:1

n-hexanes, ethyl acetate) 0.27; $[\alpha]_D$ +31.1 (*c* 0.28, MeOH); ECD (MeOH; *c* 0.9 mg/10 mL) λ (Δε) 220 (+3.2), 240 (0), 247 (−1.8), 262 (0), 285 (+0.3) nm; UV (MeOH) λ_{max} (log ε) 274 (0.19) nm; ν_{max}(film)/cm^{-1} 2926 and 2851 (CH), 1595 and 1506 (C=C), 1469, 1239, 1210, 1124 and 1010; δ_H (400 MHz; CDCl$_3$; Me$_4$Si) 1.14 (3H, d, *J* = 6.8 Hz, H-9), 3.31 (2H, d, *J* = 6.8 Hz, H-7′), 3.85 (3H, s, OMe), 3.87 (6H, s, 2 × OMe), 3.89 (3H, s, OMe), 4.58 (1H, qd, *J* = 2.4, 6.8 Hz, H-8), 5.07–5.14 (3H, m, H-7 and H-9′), 5.92–6.02 (1H, m, H-8′), 6.39 (1H, d, *J* = 2.0 Hz, H-6′), 6.52 (1H, d, *J* = 2.0 Hz, H-2′) and 6.61 (2H, s, H-2 and H-6); δ_C (100 MHz; CDCl$_3$) 12.6 (C-9), 40.0 (C-7′), 56.1 (OMe), 56.2 (OMe), 60.9 (OMe), 73.2 (C-8), 77.2 (C-7), 103.2 (C-2 and C-6), 105.1 (C-6′), 109.7 (C-2′), 115.8 (C-9′), 129.5 (C-1), 132.2 (C-4′), 132.5 (C-1′), 137.4 (C-8′), 137.7 (C-4), 143.4 (C-3′), 149.2 (C-5′) and 153.4 (C-3 and C-5); *m*/*z* (ESI+): 409 (MNa$^+$, 100%) and 360 (67); HRMS (ESI+) Found (MNa$^+$): 409.1610 C$_{22}$H$_{26}$NaO$_6$ requires 409.1622. All NMR data was in agreement with literature values.[19]

(−)-Eusiderin L, 23, and (2*R*,3*R*)-3-Methyl-2-(3′,4′,5′-trimethoxyphenyl)-5-methoxy-1,4-benzodioxane, 22. To a stirred solution of bromide **19a** (30.0 mg, 0.07 mmol) in dry THF (1.20 mL), under an atmosphere of nitrogen at −78 °C, was added *t*-BuLi (1.4 M in THF, 0.10 mL, 0.14 mmol). After 5 min, dry DMF (0.065 mL, 0.85 mmol) was added and the mixture stirred at −78 °C for 1 h and then allowed to warm to room temperature and left for a further 1 h. Sat. aq. NH$_4$Cl (3 mL) was added and the aqueous mixture extracted with ethyl acetate (3 × 8 mL). The combined organic extracts were dried (MgSO$_4$) and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (4:1 *n*-hexanes, ethyl acetate) to yield the title product **23** (19.0 mg, 73%) as a colorless oil. R_f (2:1 *n*-hexanes, ethyl acetate) 0.46; $[\alpha]_D$ −4.8 (*c* 1.70, MeOH); ECD (MeOH; *c* 1.1 mg/10 mL) λ (Δε) 220 (+3.1), 245 (+0.6), 275 (0), 305 (−0.6), 318 (0), 332 (+0.9) nm; ν_{max}(film)/cm^{-1} 2939 (CH), 1686 (C=O), 1590 and 1500 (C=C), 1463, 1326, 1228, 1124, 1102 and 728; δ_H (400 MHz; CDCl$_3$; Me$_4$Si) 1.32 (3H, d, *J* = 6.4 Hz, H-9), 3.87 (3H, s, OMe), 3.90 (6H, s, 2 × OMe), 3.97 (3H, s, OMe), 4.18–4.25 (1H, m, H-8), 4.59 (1H, d, *J* = 7.6 Hz, H-7), 6.59 (2H, s, H-2, H-6), 7.12 (1H, d, *J* = 2.0 Hz, H-6′), 7.16 (1H, d, *J* = 2.0 Hz, H-2′) and 9.80 (1H, s, CHO); δ_C (100 MHz; CDCl$_3$) 17.1 (C-9), 56.2 (OMe), 56.3 (OMe), 60.8 (OMe), 74.9 (C-8), 80.8 (C-7), 103.2 (C-6′), 104.5 (C-2 and C-6), 114.4 (C-2′), 129.2 (C-1′), 131.6 (C-1), 138.7 (C-4), 138.8 (C-4′), 144.4 (C-3′), 149.4 (C-5′), 153.6 (C-3 and C-5) and 190.7 (C-7′); *m*/*z* (ESI+): 397 (MNa$^+$, 100%) and 360 (30); HRMS (ESI+) Found (MNa$^+$): 397.1252 C$_{20}$H$_{22}$NaO$_7$ requires 397.1258. The ^{1}HNMR data was in agreement with literature values.[19] In a separate fraction, **22** (5.2 mg, 21%) was collected as a white solid. R_f (2:1 *n*-hexanes, ethyl acetate) 0.29; mp: 138.5–142 °C; $[\alpha]_D$ −9.2 (*c* 1.20, MeOH); ECD (MeOH; *c* 1.1 mg/10 mL) λ (Δε) 222 (+2.4), 234 (0), 238 (−0.3), 244 (0), 278 (+0.3) nm; UV (MeOH) λ_{max} (log ε) 272 (0.31) nm; ν_{max}(film)/cm^{-1} 2938 (CH), 1594 (C=C), 1475, 1252, 1125, 1096, 1008 and 767; δ_H (400 MHz; CDCl$_3$; Me$_4$Si) 1.27 (3H, d, *J* = 6.4 Hz, CH$_3$), 3.86 (3H, s, OMe), 3.88 (6H, s, 2 × OMe), 3.91 (3H, s, OMe), 4.11–4.15 (1H, m, H-3), 4.57 (1H, d, *J* = 7.6 Hz, H-2), 6.54 (1H, dd, *J* = 1.2, 8.0 Hz, H-6), 6.59 (2H, s, H-2′, H-6′), 6.63 (1H, dd, *J* = 1.6, 8.4 Hz, H-8), 6.79 (1H, t, *J* = 8.0 Hz, H-7); δ_C (100 MHz; CDCl$_3$) 17.3 (CH$_3$), 56.1 (OMe), 56.2 (OMe), 60.8 (OMe), 74.1 (C-3), 81.0 (C-2), 104.2 (C-6), 104.5 (C-2′ and C-6′), 109.9 (C-8), 120.2 (C-7), 132.4 (C-1′), 133.2 (C-4a), 138.5 (C-4′), 144.6 (C-8a), 148.8 (C-5) and 153.6 (C-3′ and C-5′); *m*/*z* (ESI+): 369 (MNa$^+$, 100%), 360 (30) and 347 (30); HRMS (ESI+) Found (MNa$^+$): 369.1300 C$_{19}$H$_{22}$NaO$_6$ requires 369.1309.

(2*S*,3*R*)-3-Methyl-2-(3′,4′,5′-trimethoxyphenyl)-5-methoxy-1,4-benzodioxane, 24. To a solution of bromide **19b** (23.0 mg, 0.054 mmol) in dry THF (1.00 mL) under an atmosphere of nitrogen at −78 °C was added *t*-BuLi (1.4 M in THF, 0.10 mL, 0.14 mmol) and the mixture stirred for 10 min. Sat. aq. NH$_4$Cl (3 mL) was added and the aqueous mixture extracted with ethyl acetate (3 × 8 mL). The combined organic extracts were dried (MgSO$_4$) and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (4:1 *n*-hexanes, ethyl acetate) to yield the title product **24** (15.1 mg, 81%) as a pale yellow oil. R_f (2:1 *n*-hexanes, ethyl acetate) 0.36; $[\alpha]_D$ +32.4 (*c* 0.80, MeOH); ECD (MeOH; *c* 1.1 mg/10 mL) λ (Δε) 221 (+2.0), 230 (0), 244 (−3.1), 275 (0), 283 (+0.1) nm; UV (MeOH) λ_{max} (log ε) 271 (0.41) nm; ν_{max}(film)/cm^{-1} 2938 (CH), 1593 and 1497 (C=C), 1475, 1253, 1127, 1088, 1007, 767 and 717; δ_H (400 MHz; CDCl$_3$; Me$_4$Si) 1.16 (3H, d, *J* = 6.8 Hz, CH$_3$), 3.85 (3H, s, OMe), 3.88 (6H, s, 2 × OMe), 3.90 (3H, s, OMe), 4.61 (1H, qd, *J* = 2.4, 6.8 Hz, H-3), 5.12 (1H, d, *J* = 2.4 Hz, H-2), 6.55 (1H, dd, *J* = 1.2, 8.4 Hz, H-6), 6.62 (2H, s, H-2′ and H-6′), 6.66 (1H, dd, *J* = 1.2, 8.4 Hz, H-8) and 6.81 (1H, t, *J* = 8.4 Hz, H-7); δ_C (100 MHz; CDCl$_3$) 12.6 (CH$_3$), 56.2 (OMe), 56.2 (OMe), 60.9 (OMe), 73.3 (C-3), 77.0 (C-2), 103.2 (C-2′ and C-6′), 104.6 (C-6), 110.0 (C-8), 120.0 (C-7), 131.5 (C-4a), 132.4 (C-1′), 137.8 (C-4′), 143.7 (C-8a), 149.5 (C-5) and 153.4 (C-3′ and C-5′); *m*/*z* (ESI+): 369 (MNa$^+$, 100%) and 360 (60); HRMS (ESI+) Found (MNa$^+$): 369.1304 C$_{19}$H$_{22}$NaO$_6$ requires 369.1309.

(−)-Eusiderin G, 25. To a solution of (-)-eusiderin L **23** (49.0 mg, 0.131 mmol) in dry toluene (6 mL), under an atmosphere of nitrogen at room temperature, was added (triphenylphosphoranylidene)-acetaldehyde (44.0 mg, 0.134 mmol). The solution was heated at reflux for 3 days and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (3:1 *n*-hexanes, ethyl acetate) to yield the title product **25** (13.8 mg, 27% (95% brsm.)) as a pale yellow oil. R_f (1:1 *n*-hexanes, ethyl acetate) 0.68; $[\alpha]_D$ −19.4 (*c* 0.54, MeOH); ECD (MeOH; *c* 0.9 mg/10 mL) λ (Δε) 227 (+4.4), 257 (0), 317 (−0.7), 360 (0), 380 (+0.2) nm; ν_{max}(film)/cm^{-1} 2988 and 2902 (CH), 1673 (C=O), 1591 and 1506 (C=C), 1236, 1125, 1103, 1066 and 911; δ_H (400 MHz; CDCl$_3$; Me$_4$Si) 1.30 (3H, d, *J* = 6.4 Hz, H-9), 3.87 (3H, s, OMe), 3.90 (6H, s, 2 × OMe), 3.95 (3H, s, OMe), 4.16–4.23 (1H, m, H-8), 4.58 (1H, d, *J* = 8.0 Hz, H-7), 6.57 (1H, dd, *J* = 7.6, 15.6 Hz, H-8′), 6.59 (2H, s, H-2, H-6), 6.76 (1H, d, *J* = 2.0 Hz, H-6′), 6.89 (1H, d, *J* = 2.0 Hz, H-2′) 7.34 (1H, d, *J* = 15.6 Hz, H-7′) and 9.65 (1H, d, *J* = 7.6 Hz, C-9′); δ_C (100 MHz; CDCl$_3$) 17.2 (C-9), 56.2 (OMe), 56.3 (OMe), 60.9 (OMe), 74.7 (C-8), 81.0 (C-7), 104.0 (C-6′), 104.4 (C-2 and C-6), 111.2 (C-2′), 126.5 (C-1′), 127.3 (C-8′), 131.8 (C-1), 136.1 (C-4′), 138.7 (C-4), 144.6 (C-3′), 149.1 (C-5′), 152.8 (C-7′), 153.6 (C-3 and C-5) and 193.5 (C-9′); *m*/*z* (ESI+): 423 (MNa$^+$, 100%), 360 (80) and 267 (15); HRMS (ESI+) Found (MNa$^+$): 423.1413 C$_{22}$H$_{24}$NaO$_7$ requires 423.1414. The ^{1}HNMR data was in agreement with literature values.[33] (−)-Eusiderin L **23** (35.4 mg, 0.095 mmol) was also recovered from the reaction in a separate fraction.

(−)-Eusiderin M, 5. To a solution of (−)-eusiderin G **25** (10.8 mg, 0.027 mmol) in dry methanol (2 mL), under an atmosphere of nitrogen at room temperature was added NaBH$_4$ (1.0 mg, 0.027 mmol) and the mixture stirred for 15 min. Water (2 mL) was added and the mixture was extracted with ether (3 × 5 mL). The combined organic extracts were dried (MgSO$_4$) and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (2:1 *n*-hexanes, ethyl acetate) to yield the title product **5** (10.5 mg, 96%) as a colorless oil. R_f (1:1 *n*-hexanes, ethyl acetate) 0.37; $[\alpha]_D$ −16.9 (*c* 0.77, MeOH); ECD (MeOH; *c* 1.0 mg/10 mL) λ (Δε) 229 (+2.6), 241 (0), 254 (−0.9), 304 (0), 346 (+0.1) nm; ν_{max}(film)/cm^{-1} 3517 (OH), 2942 (CH), 1593 and 1508 (C=C), 1463, 1345, 1229, 1146, 1125, 1103 and 727; δ_H (400 MHz; CDCl$_3$; Me$_4$Si) 1.27 (3H, d, *J* = 6.0 Hz, H-9), 3.86 (3H, s, OMe), 3.89 (6H, s, 2 × OMe), 3.92 (3H, s, OMe), 4.10–4.16 (1H, m, H-8), 4.30 (2H, d, *J* = 5.6 Hz, H-9′), 4.56 (1H, d, *J* = 8.0 Hz, H-7), 6.21–6.27 (1H, m, H-8′), 6.48 (1H, d, *J* = 15.6 Hz, H-7′), 6.58 (2H, s, H-2, H-6), 6.60 (1H, d, *J* = 2.0 Hz, H-6′) and 6.68 (1H, d, *J* = 2.0 Hz, H-2′); δ_C (100 MHz; CDCl$_3$) 17.3 (C-9), 56.2 (OMe), 56.2 (OMe), 60.8 (OMe), 63.7 (C-9′), 74.3 (C-8), 81.1 (C-7), 102.4 (C-6′), 104.5 (C-2 and C-6), 108.2 (C-2′), 127.2 (C-8′), 129.3 (C-1′), 131.0 (C-7′), 132.3 (C-4′), 133.0 (C-1), 138.6 (C-4), 144.4 (C-3′), 148.8 (C-5′) and 153.6 (C-3 and C-5); *m*/*z* (ESI+): 425 (MNa$^+$, 100%), 399 (40), 360 (40) and 264 (30); HRMS (ESI+) Found (MNa$^+$): 425.1584 C$_{22}$H$_{26}$NaO$_7$ requires 425.1571. The ^{1}HNMR data was in agreement with literature values except for the assignment of two protons which should be interchanged.[19]

(1*R*,2*R*)-2-(2′-(Benzyloxy)-4′-bromo-6′-methoxyphenoxy)-1-(3″,4″-methylenedioxyphenyl)propan-1-ol, 26a and (1*S*,2*R*)-2-(2′-(Benzyloxy)-4′-bromo-6′-methoxyphenoxy)-1-(3″,4″-

methylenedioxyphenyl)propan-1-ol, 26b. To a solution of aldehyde **15** (0.400 g, 1.10 mmol) in dry THF (32 mL), under an atmosphere of nitrogen at room temperature was added 3,4-methylenedioxyphenylmagnesium bromide (1.0 M in THF, 3.29 mL, 3.30 mmol) slowly. The mixture was stirred at room temperature for 22 h before sat. aq. NH_4Cl (25 mL) was added and the aqueous mixture extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo.* The crude product was purified by flash chromatography (4:1 *n*-hexanes, ethyl acetate) to yield the title product **26a** (0.310 g, 58%) as a viscous colorless oil. R_f (2:1 *n*-hexanes, ethyl acetate) 0.65; $[\alpha]_D$ +9.7 (*c* 0.60, $CHCl_3$); ν_{max}(film)/cm^{-1} 3525 (OH), 2937 (CH), 1589 and 1489 (C=C), 1445, 1416, 1224, 1115, 1039, 810 and 735; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.08 (3H, d, *J* = 6.4 Hz, H-3), 3.70 (1H, s, OH), 3.86 (3H, s, OMe), 4.30 (1H, qd, *J* = 2.4, 6.4 Hz, H-2), 4.76 (1H, d, *J* = 2.4 Hz, H-1), 5.08 (2H, s, OCH_2Ph), 5.91 (2H, s, OCH_2O), 6.67 (1H, dd, *J* = 1.6, 8.0 Hz, H-6″), 6.71 (1H, d, *J* = 8.0 Hz, H-5″), 6.77 (1H, d, *J* = 2.0 Hz, H-5′), 6.81 (1H, d, *J* = 1.6 Hz, H-2″), 6.84 (1H, d, *J* = 2.0 Hz, H-3′) and 7.33−7.38 (5H, m, Ar−H); δ_C (100 MHz; $CDCl_3$) 12.6 (C-3), 56.4 (OMe), 71.4 (OCH_2Ph) 73.1 (C-1), 82.7 (C-2), 100.8 (OCH_2O), 106.7 (C-2″), 107.9 (C-5″), 109.2 (C-5′), 110.8 (C-3′), 116.3 (C-4′), 119.1 (C-6″), 127.5 (Ar−CH), 128.3 (Ar−CH), 128.7 (Ar−CH), 133.7 (C-1″), 134.8 (C-1′), 135.9 (Ar−C), 146.4 and 147.5 (C-3″ and C-4″), 153.3 (C-2′) and 154.3 (C-6′); *m*/*z* (ESI+): 511 (^{81}BrMNa$^+$, 100%), 509 (^{79}MNa$^+$, 95), 412 (8) and 360 (13); HRMS (ESI+) Found (MNa$^+$): 511.0541 $C_{24}H_{23}{}^{81}BrNaO_6$ requires 511.0551. Found (MNa$^+$): 509.0564 $C_{24}H_{23}{}^{79}BrNaO_6$ requires 509.0570. The title product **26b** (0.134 g, 25%) was isolated in a separate fraction as a viscous colorless oil. R_f (2:1 *n*-hexanes, ethyl acetate) 0.60; $[\alpha]_D$ −72.6 (*c* 1.44, $CHCl_3$); ν_{max}(film)/cm^{-1} 3490 (OH), 2974 (CH), 1589 and 1488 (C=C), 1416, 1232, 1116, 1038, 811 and 734; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.07 (3H, d, *J* = 6.4 Hz, H-3), 3.86 (3H, s, OMe), 3.99−4.05 (1H, m, H-2), 4.41 (1H, d, *J* = 1.6 Hz, OH), 4.54 (1H, dd, *J* = 2.0, 8.4 Hz, H-1), 5.07 (2H, s, OCH_2Ph) 5.92 (2H, s, OCH_2O), 6.71 (1H, d, *J* = 8.0 Hz, H-5″), 6.75 (1H, d, *J* = 2.0 Hz, H-5′), 6.75 (1H, dd, *J* = 1.6, 8.0 Hz, H-6″), 6.79 (1H, d, *J* = 1.6 Hz, H-2″), 6.82 (1H, d, *J* = 2.0 Hz, H-3′) and 7.34−7.38 (5H, m, Ar−H); δ_C (100 MHz; $CDCl_3$) 17.3 (C-3), 56.3 (OMe), 71.5 (OCH_2Ph) 78.7 (C-1), 85.8 (C-2), 100.9 (OCH_2O), 107.5 (C-2″), 108.0 (C-5″), 109.3 (C-5′), 110.6 (C-3′), 116.1 (C-4′), 120.9 (C-6″), 127.8 (Ar−CH), 128.4 (Ar−CH), 128.7 (Ar−CH), 134.5 (C-1″), 135.8 (C-1′), 136.3 (Ar−C), 147.2 (C-3″), 147.6 (C-4″), 152.8 (C-2′) and 153.6 (C-6′); *m*/*z* (ESI+): 527 (^{81}BrMK$^+$, 100%), 525 (^{79}MK$^+$, 95) and 360 (50); HRMS (ESI+) Found (MK$^+$): 527.0281 $C_{24}H_{23}{}^{81}BrKO_6$ requires 527.0290. Found (MK$^+$): 525.0299 $C_{24}H_{23}{}^{79}BrKO_6$ requires 525.0310.

(1*R*,2*R*)-2-(4′-Bromo-2′-hydroxy-6′-methoxyphenoxy)-1-(3″,4″-methylenedioxyphenyl)propan-1-ol. To a solution of benzyl ether **26a** (0.300 g, 0.62 mmol) in ethyl acetate (30 mL) was added 37% HCl (1.5 mL) and 10% Pd/C (0.045 g) and the mixture stirred under an atmosphere of hydrogen for 1 h. The mixture was filtered through Celite and the filtrate was washed with sat. aq. $NaHCO_3$ (2 × 25 mL) and water (25 mL). The aqueous layers were further extracted with ethyl acetate (2 × 35 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo.* The crude product was purified by flash chromatography (4:1 *n*-hexanes, ethyl acetate) to yield the title product (0.140 g, 57%) as a viscous yellow oil. R_f (2:1 *n*-hexanes, ethyl acetate) 0.53; $[\alpha]_D$ +2.9 (*c* 0.76, $CHCl_3$); ν_{max}(film)/cm^{-1} 3367 (OH), 2988 (CH), 1588 and 1489 (C=C), 1444, 1250, 1223, 1105, 1038, 911, 809 and 732; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.13 (3H, d, *J* = 6.4 Hz, H-3), 3.21 (1H, br s, 1-OH), 3.80 (3H, s, OMe), 4.26 (1H, qd, *J* = 2.8, 6.4 Hz, H-2), 4.79 (1H, d, *J* = 2.8 Hz, H-1), 5.94 (2H, s, OCH_2O), 6.58 (1H, d, *J* = 2.0 Hz, H-5′), 6.72 (1H, d, *J* = 2.0 Hz, H-3′) 6.76 (2H, m, H-5″ and H-6″), 6.88 (1H, s, H-2″) and 7.67 (1H, br s, Ar−OH); δ_C (100 MHz; $CDCl_3$) 14.1 (C-3), 56.1 (OMe), 75.1 (C-1), 82.2 (C-2), 101.1 (OCH_2O), 107.2 (C-2″), 107.4 (C-5′), 108.0 (C-5″), 112.5 (C-3′), 116.8 (C-4′), 120.0 (C-6″), 132.7 (C-1′), 133.3 (C-1″), 147.2 and 147.7 (C-3″ and C-4″), 151.8 (C-2′) and 153.6 (C-6′); *m*/*z* (ESI+): 421 (^{81}BrMNa$^+$, 43%), 419 (^{79}MNa$^+$, 45) and 360 (100); HRMS (ESI+) Found (MNa$^+$): 421.0071 $C_{17}H_{17}{}^{81}BrNaO_6$ requires 421.0081. Found (MNa$^+$): 419.0093 $C_{17}H_{17}{}^{79}BrNaO_6$ requires 419.0101.

(2*R*,3*R*)-3-Methyl-2-(3′,4′-methylenedioxyphenyl)-7-bromo-5-methoxy-1,4-benzodioxane, 27a, and (2*S*,3*R*)-3-Methyl-2-(3′,4′-methylenedioxyphenyl)-7-bromo-5-methoxy-1,4-benzodioxane, 27b. To a solution of (1*R*,2*R*)-2-(4′-bromo-2′-hydroxy-6′-methoxyphenoxy)-1-(3″,4″-methylenedioxyphenyl)propan-1-ol (110 mg, 0.277 mmol) and Amberlyst 15 (0.020 g) in dry toluene (6 mL), under an atmosphere of nitrogen, was heated at reflux for 18 h. The solution was filtered and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (9:1 *n*-hexanes, ethyl acetate) to yield the title product **27a** (67.1 g, 64%) as a pale yellow oil. R_f (3:1 *n*-hexanes, ethyl acetate) 0.65; $[\alpha]_D$ −2.5 (*c* 1.48, MeOH); ECD (MeOH; *c* 1.1 mg/10 mL) λ ($\Delta\varepsilon$) 222 (+3.4), 237 (0), 245 (−0.9), 260 (0), 270 (+0.1), 275 (0), 288 (−0.7), 299 (0) nm; UV (MeOH) λ_{max} (log ε) 286 (1.24) nm; ν_{max}(film)/cm^{-1} 2973 (CH), 1598 and 1490 (C=C), 1443, 1241, 1220, 1143, 1104, 1037, 809 and 730; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.23 (3H, d, *J* = 6.4 Hz, CH_3), 3.87 (3H, s, OMe), 4.02−4.09 (1H, m, H-3), 4.54 (1H, d, *J* = 8.0 Hz, H-2), 5.99 (2H, s, OCH_2O), 6.64 (1H, d, *J* = 2.4 Hz, H-6), 6.76 (1H, d, *J* = 2.4 Hz, H-8) and 6.82−6.83 (3H, m, H-2′, H-5′ and H-6′); δ_C (100 MHz; $CDCl_3$) 17.1 (CH_3), 56.3 (OMe), 74.2 (C-3), 80.8 (C-2), 101.3 (OCH_2O), 107.5 (C-2′), 107.9 (C-5′), 108.4 (C-6), 112.1 (C-7), 113.0 (C-8), 121.5 (C-6′), 130.2 (C-1′), 132.4 (C-4a), 145.1 (C-8a), 148.1 and 148.2 (C-3′ and C-4′) and 149.2 (C-5); *m*/*z* (ESI+): 403 (^{81}BrMNa$^+$, 26%), 401 (^{79}MNa$^+$, 25), 360 (100) and 331 (30); HRMS (ESI+) Found (MNa$^+$): 402.9970 $C_{17}H_{15}{}^{81}BrNaO_5$ requires 402.9975. Found (MNa$^+$): 400.9989 $C_{17}H_{15}{}^{79}BrNaO_5$ requires 400.9995. In a separate fraction, title product **27b** (13.4 mg, 13%) was also isolated, as a yellow oil. R_f (3:1 *n*-hexanes, ethyl acetate) 0.61; $[\alpha]_D$ +36.2 (*c* 0.32, MeOH); ECD (MeOH; *c* 0.9 mg/10 mL) λ ($\Delta\varepsilon$) 220 (+4.3), 240 (0), 247 (−1.7), 257 (0), 286 (+1.5) nm; UV (MeOH) λ_{max} (log ε) 286 (0.82) nm; ν_{max}(film)/cm^{-1} 2935 (CH), 1597 and 1492 (C=C), 1444, 1241, 1117, 1039 and 811; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.13 (3H, d, *J* = 6.4 Hz, CH_3), 3.88 (3H, s, OMe), 4.54 (1H, qd, *J* = 2.4, 6.4 Hz, H-3), 5.09 (1H, d, *J* = 2.4 Hz, H-2), 5.97 (2H, s, OCH_2O), 6.66 (1H, d, *J* = 2.0 Hz, H-6), 6.80 (1H, d, *J* = 2.0 Hz, H-8), 6.82 and 6.82 (2H, br s, H-5′ and H-6′) and 6.86 (1H, s, H-2′); δ_C (100 MHz; $CDCl_3$) 12.9 (CH_3), 56.4 (OMe), 73.2 (C-3), 77.2 (C-2), 101.2 (OCH_2O), 106.8 (C-2′), 108.2 (C-6), 108.3 (C-5′), 112.1 (C-7), 113.1 (C-8), 119.9 (C-6′), 130.1 (C-1′), 130.9 (C-4a), 144.2 (C-8a), 147.5 and 147.9 (C-3′ and C-4′) and 149.8 (C-5); *m*/*z* (ESI+): 403 (^{81}BrMNa$^+$, 33%), 401 (^{79}MNa$^+$, 34), 360 (100) and 331 (30); HRMS (ESI+) Found (MNa$^+$): 402.9971 $C_{17}H_{15}{}^{81}BrNaO_5$ requires 402.9975. Found (MNa$^+$): 400.9988 $C_{17}H_{15}{}^{79}BrNaO_5$ requires 400.9995.

(−)-Eusiderin B, 2. To a solution of bromide **27a** (25.0 mg, 0.066 mmol) in dry THF (2 mL), under an atmosphere of nitrogen, was added allyl boronic acid pinacol ester **21** (0.019 mL, 0.099 mmol), CsF (40.0 mg, 0.264 mmol) and $Pd(PPh_3)_4$ (0.6 mg, 0.007 mmol) and the mixture was heated at reflux for 16 h. The reaction was then cooled to room temperature and ethyl acetate (2 mL) was added, followed by brine (2 mL). The organic layer was separated and the aqueous layer further extracted with ethyl acetate (2 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (4:1 *n*-hexanes, ethyl acetate) to yield the title product (−)-**2** (1.6 mg, 70% brsm.) as a colorless oil. Bromide **27a** (22.5 mg), was also recovered. R_f (3:1 *n*-hexanes, ethyl acetate) 0.65; $[\alpha]_D$ −2.3 (*c* 0.80, MeOH); ECD (MeOH; *c* 0.8 mg/10 mL) λ ($\Delta\varepsilon$) 220 (+2.8), 234 (0), 240 (−1.1), 250 (0), 263 (+0.2), 275 (0), 287 (−0.5), 298 (0) nm; UV (MeOH) λ_{max} (log ε) 285 (1.07) nm; ν_{max}(film)/cm^{-1} 2923 (CH), 1599 and 1507 (C=C), 1446, 1240, 1149, 1103, 1038, 935 and 814; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.23 (3H, d, *J* = 6.4 Hz, H-9), 3.28 (2H, d, *J* = 6.8 Hz, H-7′), 3.88 (3H, s, OMe), 4.03−4.10 (1H, m, H-8), 4.55 (1H, d, *J* = 8.0 Hz, H-7), 5.04−5.12 (2H, m, H-9′), 5.89−5.97 (1H, m, H-8′), 5.99 (2H, s, OCH_2O), 6.36 (1H, d, *J* = 2.0 Hz, H- 6′), 6.45 (1H, d, *J* = 2.0 Hz, H-2′), 6.83−6.84 (3H, m, H-2, H-5 and H-6); δ_C (100 MHz; $CDCl_3$) 17.2 (C-9), 40.0 (C-7′), 56.1 (OMe), 74.1 (C-8), 80.7 (C-7), 101.3 (OCH_2O), 104.6 (C-6′), 107.6 (C-2), 108.4 (C-5), 109.6

(C-2′), 115.8 (C-9′), 121.5 (C-6), 130.9 (C-1), 131.3 (C-4′), 132.4 (C-1′), 137.3 (C-8′), 144.4 (C-3′), 148.1 (C-3 and C-4) and 148.5 (C-5′); *m/z* (ESI+): 363 (MNa^+, 80%), 360 (100), 341 (MH^+, 66) and 338 (60); HRMS (ESI+) Found (MNa^+): 363.1195 $C_{20}H_{20}NaO_5$ requires 363.1203. All NMR data was in agreement with literature values.[34]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The ^{1}H and ^{13}C NMR spectra for all compounds and the ECD spectra of compounds **1, 2, 5, 19a, 19b, 20, 22, 23, 24, 25, 27a** and **27b**. 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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