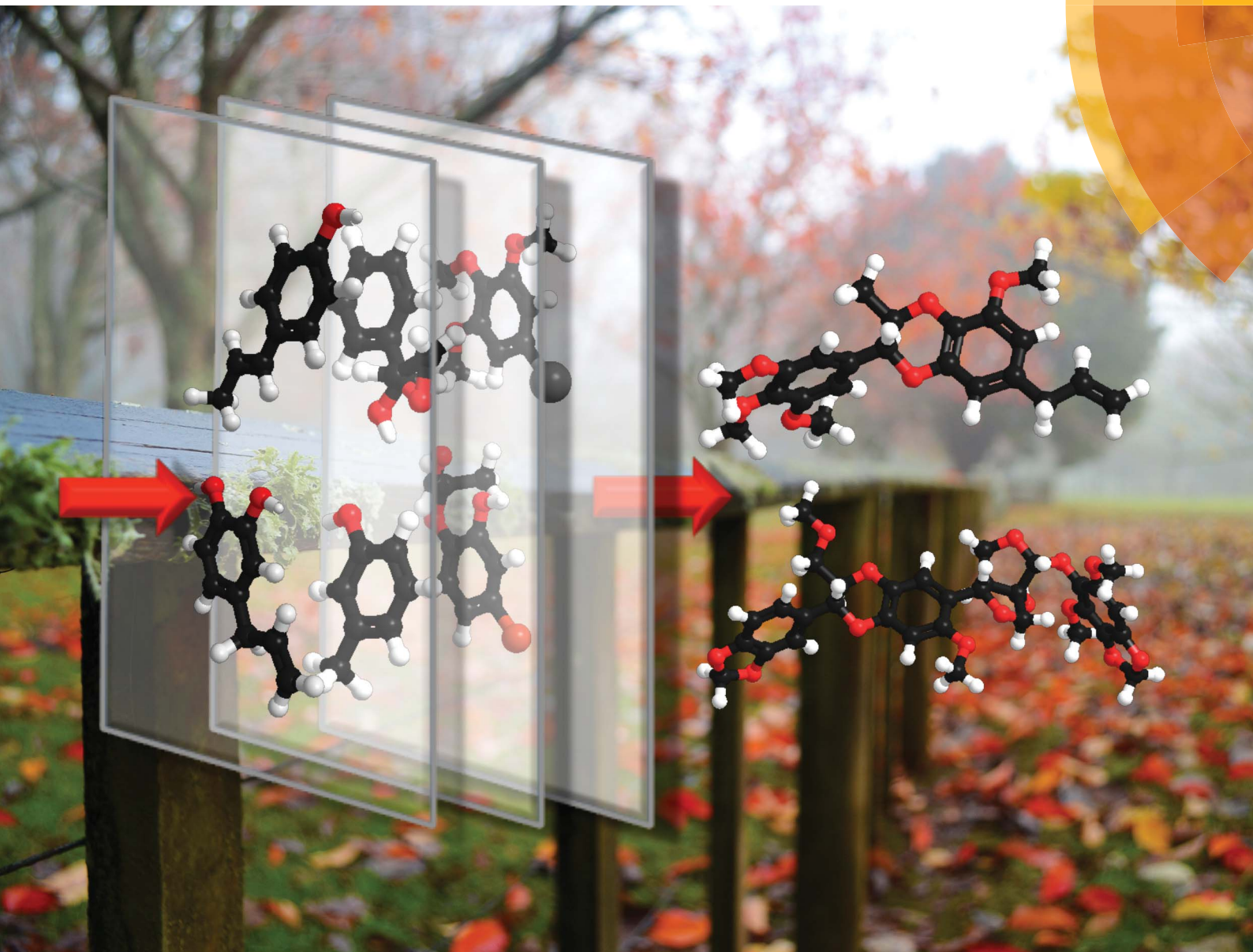


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Synthesis and biology of 1,4-benzodioxane lignan natural products



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Lignan-derived 1,4-benzodioxane natural products have been shown to exhibit a diverse array of biological activities, which has lent them to be the focus of a wealth of synthetic attention. Herein we review the background, bioactivities, biosynthesis and synthetic approaches to the 1,4-benzodioxane lignan scaffold, with an emphasis on 1,4-benzodioxane oxyneolignans.

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1 Introduction

1,4-Benzodioxane lignans are a group of natural products that exhibit a wide range of interesting biological activities which has resulted in them receiving much synthetic attention over the years. The intent of this review is to provide detailed analysis of the background, biological activity, biosynthesis and the various methods developed towards the synthesis of these compounds. There has previously been limited discussion, and review, of these natural products,^{1,2} as such, it was decided to produce a comprehensive review on these previous syntheses of 1,4-benzodioxane lignans.

The syntheses of 1,4-benzodioxane compounds can be categorised into groups subject to their general approach to construct the 1,4-benzodioxane structure. The aim of the synthetic section of this review is to provide an overview of these approaches to the synthesis of 1,4-benzodioxanes, showing the main methodologies to form these compounds, as well as other novel approaches that have been attempted. The intent is to particularly highlight the synthesis of natural 1,4-benzodioxane oxyneolignans and analogues thereof. There is reference,

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however to studies towards other 1,4-benzodioxane-containing natural products where appropriate.

1.1 Nomenclature and numbering

1,4-Benzodioxanes are subject to two different numbering systems mandated by traditional and lignan IUPAC nomenclature (Fig. 1). In this review, 1,4-benzodioxane compounds that do not have carbon sidechains representing C-7' to C-9' (e.g. **1**), are numbered in accordance to traditional IUPAC conventions. Compounds that do have a three carbon sidechain (e.g. eusiderin A (**2**)) are classified as lignan compounds and as such, each lignan fragment is numbered from C-1 to C-9.³

This review also refers to 2-aryl- and 3-aryl-1,4-benzodioxanes, numbered using the traditional IUPAC system (Fig. 2). 3-Aryl-1,4-benzodioxanes (e.g. **1** and oxyneolignan isoamericanin A (**3**)) are the most abundant type of 1,4-benzodioxane lignan found in

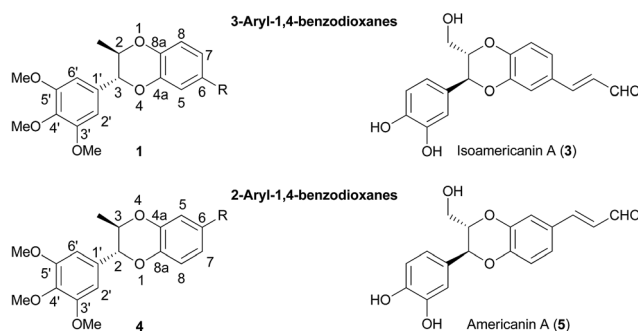


Fig. 2 The differing structures of 2-aryl- and 3-aryl-1,4-benzodioxanes.

nature; 2-aryl-1,4-benzodioxanes (e.g. **4**) are significantly less common, but some examples have been isolated, one of the most notable of which being oxyneolignan, americanin A (**5**).

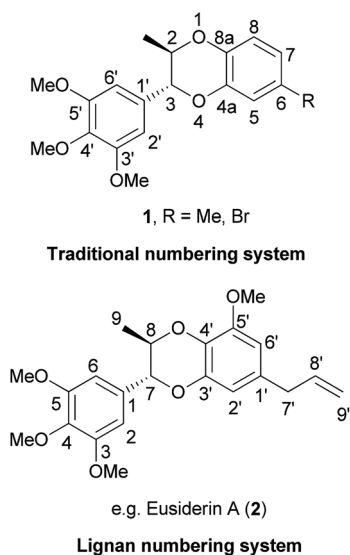


Fig. 1 The two systems used in numbering 1,4-benzodioxanes.

1.2 1,4-Benzodioxanes – oxyneolignans, flavonolignans, coumarinolignans, stillbenolignans

Naturally occurring, lignan-derived (containing a characteristic phenylpropanoid, C-6 to C-3, unit) 1,4-benzodioxane lignans can be categorised into different groups, based on the partner subclass to which their structure belongs.

1.2.1 1,4-Benzodioxane oxyneolignans. The most common type of natural 1,4-benzodioxane lignan have a second phenylpropanoid partner and are 1,4-benzodioxane oxyneolignans, e.g. eusiderin A (**2**), isoamericanin A (**3**) and americanin A (**5**), and are the main focus of this review. The biosynthesis is proposed to be the oxidative dimerization of two phenylpropanoid units (Scheme 1, see Section 3.1 for further discussion).

1.2.2 1,4-Benzodioxane flavonolignans. Flavonoids are a large class of secondary metabolites that exist in most plants and are the most common metabolites eaten by humans. Owing to their beneficial effects, their dietary uptake has increased over recent years.⁴ Encompassed in the broad class of flavonoids



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David Barker was born in Altrincham, UK. After moving to Australia, he graduated from the University of Sydney with a BSc degree (Honours, First Class) and then completed his PhD in 2002 at the same university. After post-doctoral research at the School of Medical Sciences at the University of New South Wales working with Prof. Larry Wakelin, in 2004 he joined the University of Auckland as a

lecturer. He is currently Senior Lecturer in Organic and Medicinal Chemistry and he has a diverse range of synthetic interests including biologically active natural products, drug discovery and development of novel polymeric scaffolds.

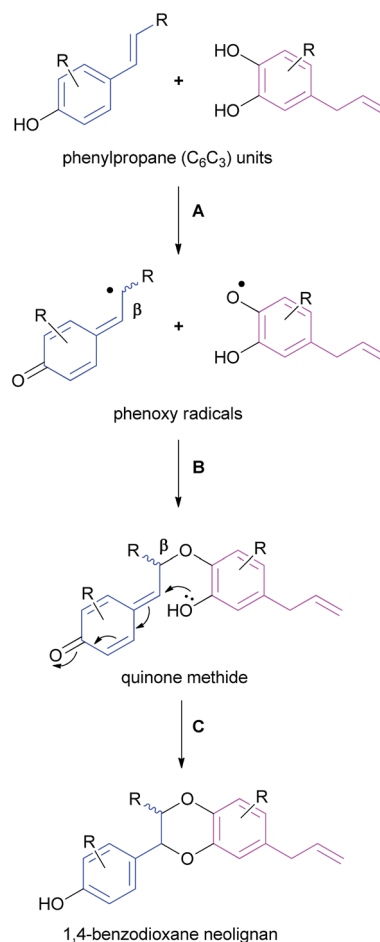


is a small subclass of compounds previously defined as, and also called here, flavonolignans. As their name suggests, they contain both a phenylpropanoid and a flavone component.⁴ 1,4-Benzodioxane flavonolignans differ in structure from 1,4-benzodioxane oxyneolignans by the presence of an affixed chromanone group in place of the phenylpropanoid partner group of the oxyneolignans (Fig. 3). Flavonolignans are biosynthetically produced by the oxidative coupling of a flavonoid (e.g. taxifolin **6**) and a phenylpropanoid (in most cases coniferyl alcohol **7**, Fig. 3; see Section 3.1, Scheme 1 for oxidative coupling mechanism).⁵

Flavonolignans were first discovered in the seeds of *Silybum marianum*, commonly known as milk thistle. The original flavonolignan to be discovered was silybin **8** (Fig. 3), and to this day it remains by far the most researched flavonolignan and 1,4-benzodioxane lignan.^{4,6–8} For more information on silybin, see the recent review by Biedermann *et al.*⁴

1.2.3 1,4-Benzodioxane coumarinolignans. Coumarinolignans are formed by the oxidative coupling of a coumarin (itself known to be formed through the cyclisation of a cinnamic acid) and an appropriate phenylpropene unit (Fig. 4).^{9,10} All known isolated coumarinolignans are 1,4-benzodioxane compounds.⁹

Cleomiscosin A (**9**), isolated from the seeds of *Cleome viscosa* and its regioisomer cleomiscosin B (**10**) were the first regioisomeric pair of 1,4-benzodioxane coumarinolignans to be found.^{9,11,12} They are both formed by the oxidative coupling of coniferyl alcohol **7** and coumarin **11**, the orientation of the dimerization determining which regioisomer is formed (Fig. 4).



Scheme 1 Proposed biosynthesis of 1,4-benzodioxanes.

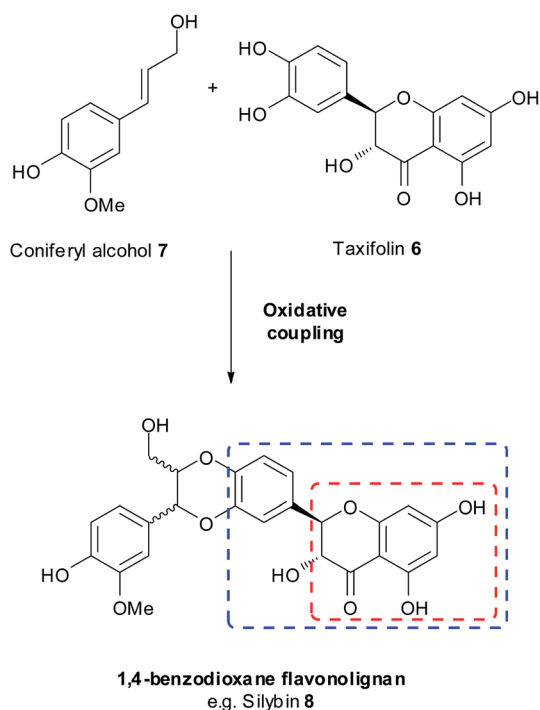


Fig. 3 Biosynthesis of flavonolignans and highlighted structural terms; the flavone nucleus is in the blue rectangle, while the chromanone is in the red rectangle.

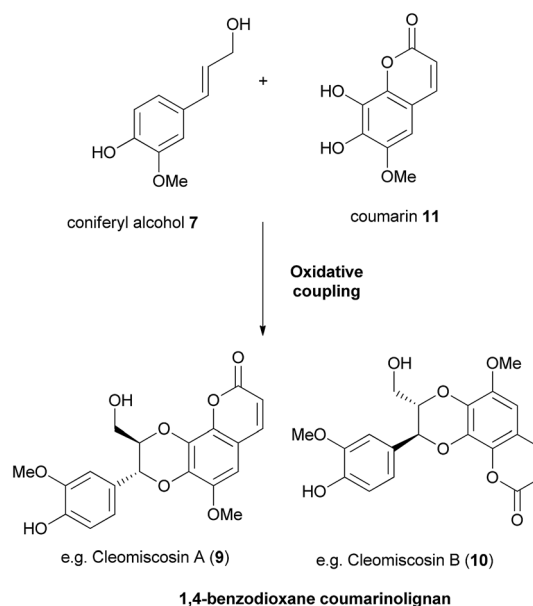


Fig. 4 Biosynthesis of coumarinolignans.



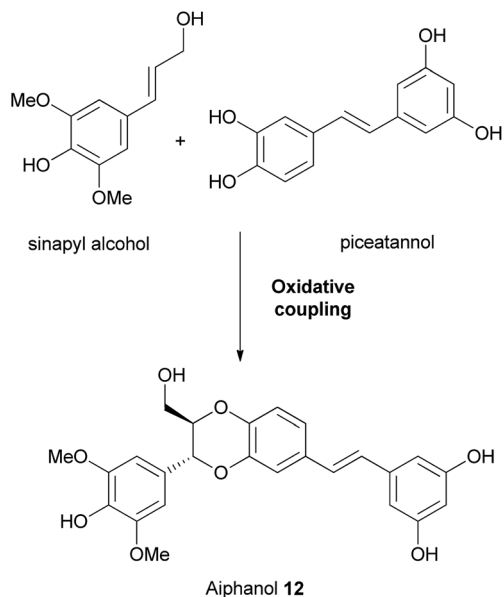


Fig. 5 Biosynthesis of aiphanol 12.

1.2.4 1,4-Benzodioxane stilbenolignans. Aiphanol 12, isolated from *Aiphanes aculeata* and formed by the oxidative dimerization of piceatannol and sinapyl alcohol (Fig. 5), is the most well-known 1,4-benzodioxane stilbenolignan,^{9,13} a hydroxylated¹⁴ and one reduced derivative have also been isolated.¹⁵

2 Bioactivities of 1,4-benzodioxane-containing natural products and MOA studies

Of all 1,4-benzodioxane lignans, the biological activities of 1,4-benzodioxane flavonolignans have been most extensively

investigated. 1,4-Benzodioxane flavonolignans, particularly silybin 8 display a range of activities that are exploited through the use of milk thistle extract, readily available to millions worldwide. There are a number of comprehensive reviews that summarise the several hundred studies that have been reported on these activities that include hepatoprotective, anticancer and antioxidant activities, along with various others that offer silybin 8 and related flavonolignans the distinction of being one of the most sought-after compounds for potential pharmaceutical applications.^{4,5,16–18}

2.1 Hepatoprotective activities

The hepatoprotective properties of silybin 8 and associated flavonolignans are well-documented, and up until recently, this biological property has been thought to be present by virtue of the chromanone functionality present in these compounds (see Fig. 3).¹⁹ HCV (Hepatitis C Virus) is a worldwide cause of chronic liver disease, with over 70% of HCV-infected patients developing a chronic condition.²⁰ This has resulted in silybin being used to treat HCV-induced liver disease. Earlier this year, it was reported that several 1,4-benzodioxane oxyneolignans – members of the rogersinine family (compounds 13–16) were found to exhibit anti-HCV activity, by analysing the reduction in expression of HCV non-structural proteins NS3 and NS5A (Fig. 6).²¹ This activity was independent of cytotoxicity.

2.2 Prostaglandin I₂ inducer activity

Isoamericanin A (3) was first isolated in 1987 by Hasegawa *et al.*²² from *Phytolacca americana* and was found to be a prostaglandin I₂ inducer – increasing the release of prostaglandin I₂ from rat aorta by up to 149.8% at 10^{−5} M concentrations.²²

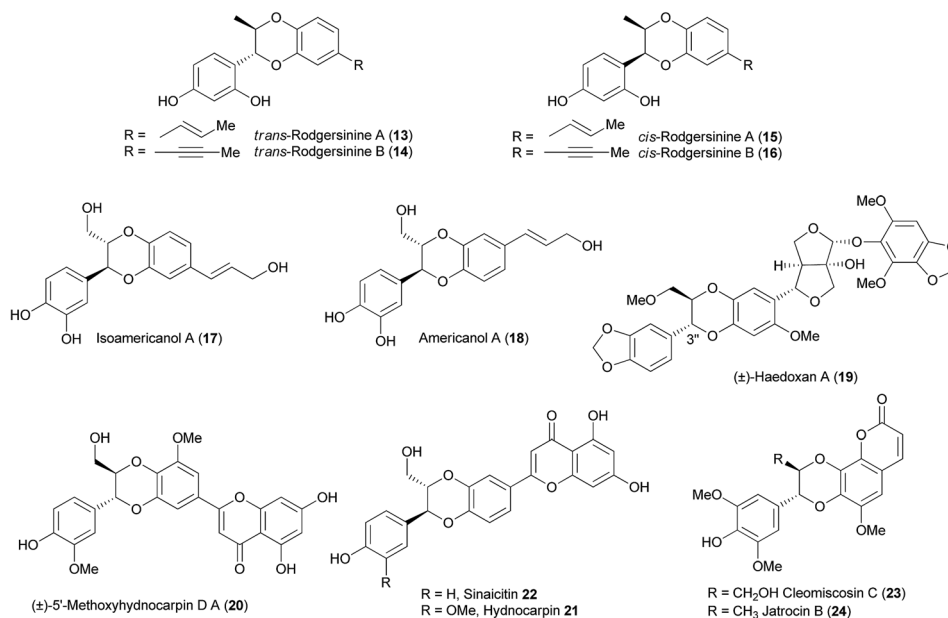


Fig. 6 Structures of natural 1,4-benzodioxane lignans.



2.3 Neurotrophic (ChAT) activity

The structurally similar isoamericanol A (**17**) was isolated five years later from the same plant by the same group.²³ Both of these compounds **3** and **17**, were isolated with their associated regioisomers americanin A (**5**) and americanol A (**18**) respectively, and have since been isolated from an array of trees and plants.^{24–26} Americanol A (**18**) and isoamericanol A (**17**) were discovered (along with isoamericanin A (**3**)) to exhibit interesting neurotrophic properties; they promoted the neurite outgrowth and enhancement of choline acetyltransferase (ChAT) activity in the primary neuronal cell cultures of fetal rat cerebral hemisphere.²³ These compounds significantly enhanced the neurite sprouting morphologically and increased the ChAT activity at 10^{-5} M concentrations. When compounds that are considered the monomeric units of these active 1,4-benzodioxane lignans were tested for their activity, they failed to enhance ChAT activity at the same concentration, and in fact cinnamic acid decreased ChAT activity. This indicated that a dimeric structure, namely the 1,4-benzodioxane moiety, is required for this neurotrophic activity.

2.4 Insecticidal activity

Haedoxan A (**19**), isolated from an extract of *Haedokusou* (*Phryma leptostachya* L.) shows remarkably high toxicity against houseflies (LD_{50} 0.25 ng by topical administration).^{27,28} In light of this potent activity, a number of SAR studies have identified structural features that are critical for the insecticidal activity of haedoxan A (**19**). Alteration of the 1,4-benzodioxane moiety in haedoxan A (**19**) resulted in complete loss or significant decrease in activity.^{29,30} Replacement of the 3''-aryl group with methyl and butyl groups also lowered the activity of the analogues, indicating that an aromatic substituent at the 3'' position may be necessary for insecticidal activity.²⁸

2.5 COX-1 and COX-2 inhibition

(–)-Aiphanol (**12**) shows potent inhibition of the cyclooxygenase enzymes, COX-1 and COX-2 with IC_{50} values of 1.9 and 9.9 μ M, respectively.³¹ In contrast, the racemic mixture of (\pm)-aiphanol (**12**) exhibits a strong inhibition of COX-2 (IC_{50} 0.17 μ M) but only a modest inhibitor of COX-1 (IC_{50} 7.3 μ M), which suggests that (+)-aiphanol (**12**) could be a more potent COX-2 inhibitor.³²

2.6 Anti-angiogenic activity

The anti-angiogenic activity of (\pm)-aiphanol (**12**) has also been studied, using an *in vitro* angiogenesis assay. The results showed that (\pm)-aiphanol (**12**) completely inhibited blood vessel growth at 100 μ g mL^{–1} and 42% inhibition at 10 μ g mL^{–1}.³² It was also noted that (\pm)-aiphanol (**12**) was more active than PI-88, an oligosaccharide which exhibits anti-angiogenic properties and was in clinical development as an agent for the treatment of certain cancers.

2.7 MDR pump inhibition activity

Flavonolignan (\pm)-5-methoxyhydnocarpin D (**20**), isolated from *Berberis fremontii* is a potent NorA MDR (Multi Drug Resistance)

pump inhibitor.³³ While (\pm)-5-methoxyhydnocarpin D (**20**) alone does not exhibit antibiotic activity, when it was used with subinhibitory concentrations of berberine it completely inhibited the growth of *S. aureus*. Silybin **8** was also found to act as a synergist with berberine, however it was not as active as (\pm)-5-methoxyhydnocarpin D (**20**) (10 μ g mL^{–1} vs. 1.2 μ g mL^{–1}).³³ (\pm)-5-Methoxyhydnocarpin D (**20**) was also shown to enhance the activity of a range of antibiotic compounds including norfloxacin (2-fold) and pentamidine (>12-fold), against *S. aureus*.³⁴

2.8 Anti-cancer activity

Hydnocarpin (**21**) and sinaicitin (**22**) (the 3''-demethoxy derivative of hydnocarpin (**21**)), flavonolignans isolated from *Sinaiticum* leaves found in the Sinai region of Egypt, have shown to have significant inhibitory activities against the murine lymphocytic leukaemia P-388 cell line (ED_{50} = 1.2 and 7.7 μ g mL^{–1}).³⁵ Hydnocarpin (**21**) has also been shown to have significant activity against six human cancer cell lines and the murine cell line, L-1210. Cleomiscosin A (**9**) has also been shown to be active against the P-388 cell line (ED_{50} = 0.4 μ g mL^{–1}),³⁶ and other 1,4-benzodioxane coumarinolignans have shown additional anti-proliferative activities in carcinoma, CNS and breast cancer cell lines.^{37,38}

2.9 Anti-oxidant activity

Natural products cleomiscosin C (**23**) and jatrocinn B (**24**) showed lipid peroxidation inhibitory activity in rat liver microsomes (IC_{50} = 0.7 and 1.4 μ g mL^{–1}, respectively) – values that are comparable to vitamin E (IC_{50} = 0.8 μ g mL^{–1}).³⁹ Additionally, cleomiscosins A (**9**) and C (**23**) have been tested for their inhibition of LDL (low-density lipoprotein) oxidation.⁴⁰ Cleomiscosin C (**23**) was found to dose-dependently inhibit LDL oxidation by either catalytic copper ions or free radicals generated by APBH. Electrophoretic analysis determined that cleomiscosin C (**23**) protects apolipoprotein B-100 against Cu²⁺-induced fragmentation (63.5% inhibition at 5.0 pM) and fluorescence analysis indicated that both cleomiscosin A (**9**) and C (**23**) protect apolipoprotein B-100 against oxidative modification by either Cu²⁺ and HOCl. This suggests that these natural products could be beneficial in preventing LDL oxidation in atherosclerotic lesions.^{40–42}

2.10 Additional activities

An aiphanol derivative has been shown to have inhibitory activity against α -glucosidase and has potential for the development of hypoglycaemic treatments.¹⁴ Other 1,4-benzodioxane compounds have shown a range of biological properties. Compounds containing the 1,4-benzodioxane moiety have demonstrated activity as selective α_{1D} -AR (adrenoreceptor) antagonists indicating the potential to act as anti-hypertensive agents. They have also been reported to act as 5-HT_{1A} receptor agonists which may have use as antidepressant and neuro-protective agents.^{43–54} Additionally, 1,4-benzodioxanes have been found to inhibit 5-lipoxygenase, an activity which presents these compounds as potential anti-inflammatory agents, with

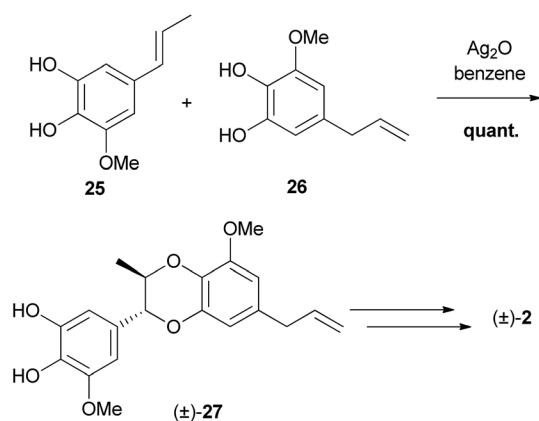


use in the treatment of asthma, rheumatoid arthritis and inflammatory bowel disease.⁵⁵ A close analogue of natural 1,4-benzodioxane oxyneolignans showed anti-*Leishmania donovani* promastigote activity, indicating possible activity against Leishmaniasis.⁵⁶ Pyrrolidynylbenzodioxanes have been shown to have affinities for $\alpha 4\beta 2$ and $\alpha 7$ central nicotinic receptors which play a key role in a wide range of CNS functions,⁵⁷ and some 1,4-benzodioxanes have been shown to exhibit anti-platelet aggregation and organ-protective activities.⁵⁸

3 Biosynthesis of 1,4-benzodioxane oxyneolignans

3.1 Proposed mechanism of biosynthesis

1,4-Benzodioxane oxyneolignans are believed to be formed by the phenolic coupling of two C_6C_3 units through a three-step process – (A) enzymatically-promoted phenol oxidation of the two phenylpropane units, (B) *O*- β coupling of the resulting phenoxy radicals and (C) cyclisation of the quinone methide system (Scheme 1).^{59–61}



Scheme 2 First synthesis of a 1,4-benzodioxane lignan, by Merlini and Zanarotti.⁶³

1,4-Benzodioxane lignan natural products are usually found as racemic mixtures; steps B and C may not be enzymatically controlled and therefore for the most part a mixture of stereo- and regioisomers are formed.⁶² There is, however an important collective of 1,4-benzodioxanes, most notably the eusiderin and rogersinine families that are found as single enantiomers in nature – resulting from a stereoselective coupling in step B. Most natural products have a *trans* configuration across the 1,4-benzodioxane (as displayed in eusiderin A (2) and iso-americanol A (17)) although some *cis* natural products (*e.g.* *cis*-rogersinine B (16)) have been isolated – an observation that is consistent with the thermodynamic control of step C.⁵⁹

3.2 Initial investigation into the biomimetic synthesis

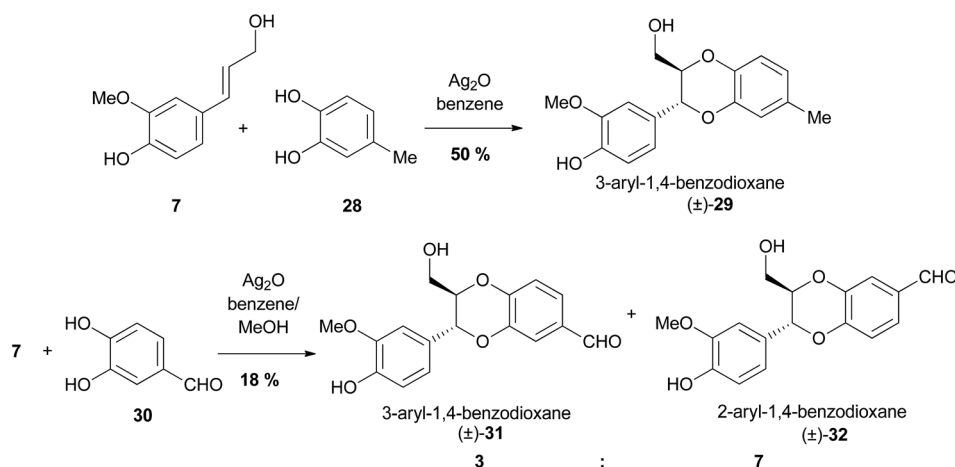
The synthesis of (±)-eusiderin A (2) by Merlini and Zanarotti in their efforts to test the postulated biosynthetic mechanism by which these compounds were hypothesised to form, constituted the first synthesis of a 1,4-benzodioxane lignan (Scheme 2).⁶³

This straightforward method, used silver(I) oxide in benzene to couple phenols 25 and 26, giving 1,4-benzodioxane (±)-27, provided the basis for a simple method by which a large number of products could be produced.

3.3 Further developments and application of biomimetic methods

Following the pioneering study by Merlini and Zanarotti, a number of investigations were conducted to determine the regioselectivity of these cross-coupling reaction to form either 2- or 3-aryl-1,4-benzodioxanes (Scheme 3).^{64,65}

It was revealed that the substituents on the catechol fragment (*i.e.* 28 in Scheme 3) have a strong effect on the regioselectivity of the reaction; electron donating substituents, like methyl as in 28, strongly favour the formation of 3-aryl products (*e.g.* (±)-29), which are by far the most commonly found in nature. The reaction is less selective and lower yielding when electron-withdrawing substituents (*e.g.* a formyl group) are present, giving both 2- and 3-aryl products, as demonstrated by



Scheme 3 The effect of substituents on the regioselectivity of oxidative dimerisation to form 1,4-benzodioxane products.⁶⁵

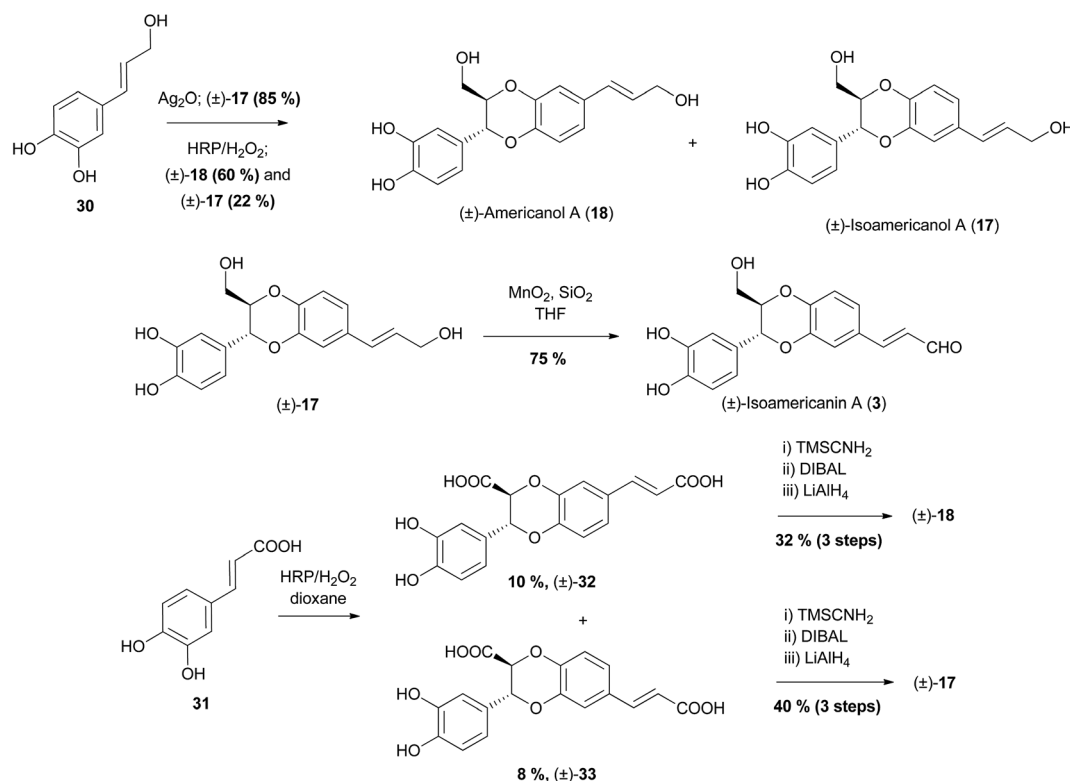


the reaction of **7** and **30** to give both the 3-aryl (\pm)-**31** and 2-aryl (\pm)-**32** 1,4-benzodioxanes in a 3 : 7 ratio.

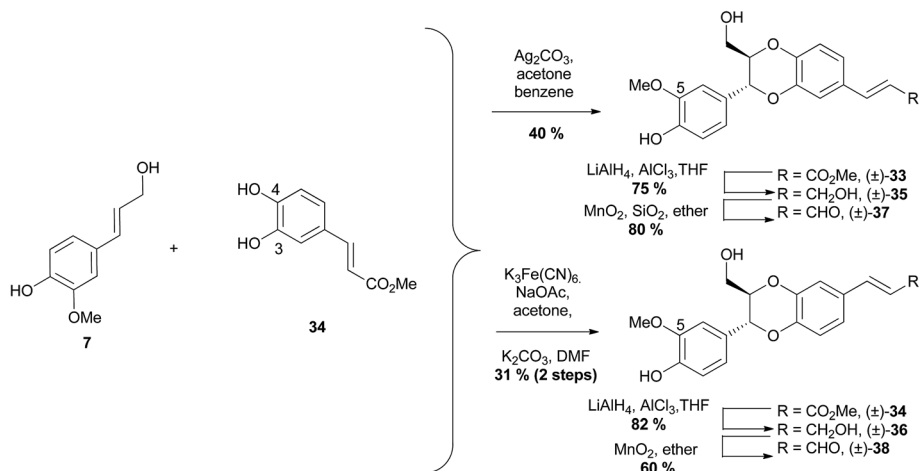
Oxidative dimerisation has been the prevailing method in synthesis of 2- or 3-hydroxymethyl-1,4-benzodioxanes, particularly that of members of the (iso)americanin family; isoamericanin A (**3**) and isoamericanol A (**17**) (3-aryl-1,4-benzodioxanes) and their corresponding regioisomers, americanin A (**5**) and americanol A (**18**) (2-aryl-1,4-benzodioxanes). Americanin A (**5**)⁶⁶ was the first of the americanin family to be isolated. Initially, it was given the structure now attributed

to isoamericanin A (**3**), however this was later revised.⁶⁷ The 2- and 3-aryl regioselectivity of conditions and starting materials have been investigated and exploited to obtain desired products (Scheme 4).^{68–70}

The oxidative homocoupling of alcohol **30** has been effected by two oxidising agents with differing results. Initially, She *et al.* effected the coupling using Ag_2O , obtaining only (\pm)-isoamericanol A (**17**) in 85% yield, which they were able to oxidise to (\pm)-isoamericanin A (**3**), using MnO_2 in the presence of silica gel.⁶⁹ Following this, Takahashi *et al.* used an alternative

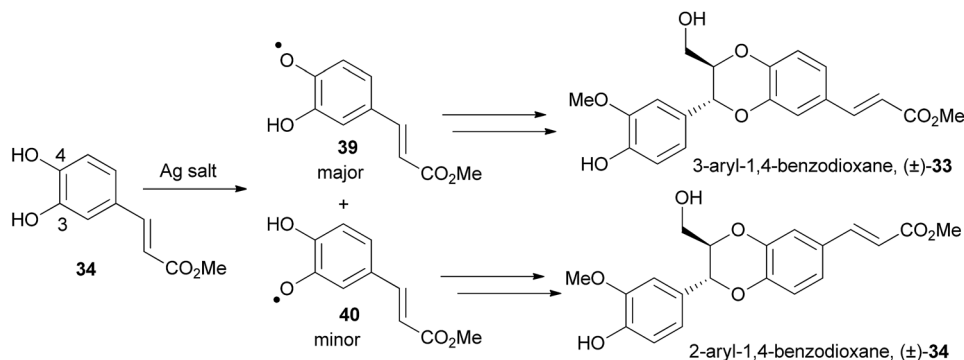


Scheme 4 Biomimetic syntheses of (\pm)-isoamericanol A (**17**), (\pm)-isoamericanin A (**3**) and (\pm)-americanol A (**18**).^{68–70}



Scheme 5 Biomimetic synthesis of methyl ethers of the (iso)americanin family.^{71,72}





Scheme 6 Regioselectivity of oxidative dimerisation when using silver salts.

oxidant, horseradish peroxidase (HRP)/H₂O₂ to give a mixture of (±)-18 and (±)-17 in an approximate 3 : 1 ratio in 82% yield.⁶⁸ When caffeic acid **31** was coupled with HRP/H₂O₂ a mixture of regioisomers (±)-32 and (±)-33 was isolated (among many other products). These were able to be converted to (±)-americanol A (**18**) and (±)-isoamericanol A (**17**) through conversion to the corresponding methyl diesters, followed by reduction.

As demonstrated in the above syntheses, the products of each reaction not only depend on the substituents on the aromatic ring, but also on the oxidative agents used in the coupling. This is particularly highlighted by She and co-workers in their synthesis of methyl ether analogues of members of the (iso)americanin families (Scheme 5).^{71,72}

By changing oxidising agents to couple phenylpropene **7** and catechol **34**, different regioselectivity of products was achieved. Using silver carbonate as the oxidising agent produced 3-aryl-1,4-benzodioxane (±)-33 in high regioselectivity of ~30 : 1 over the regioisomer (±)-34; this was in higher selectivity than the 20 : 1 mixture reported by Merlini *et al.*^{65,71} In contrast, when the same coupling reaction was performed using potassium hexacyanoferrate(III), the 2-aryl-1,4-benzodioxane (±)-34 was produced exclusively, albeit in a mixture of *trans* and *cis* isomers.⁷² This mixture was stirred with K₂CO₃ in DMF to effect isomerisation, giving the pure *trans* over the two steps. Reduction of esters (±)-33 and (±)-34 with LiAlH₄ to give (±)-35 and (±)-36, followed by oxidation with MnO₂ produced (±)-5-*O*-methyl-isoamericanin A (**37**) and (±)-5-*O*-methyl americanin A (**38**) respectively.

There was no explanation given by She *et al.* for the contrasting results achieved when using silver and iron salts, however Sefkow proposes an explanation for the difference.² Sefkow postulates that the basic silver salts slowly deprotonate the phenol groups on the catechol (*e.g.* **34**), with the more acidic phenol at C-4 deprotonating faster than the less acidic phenol at C-3, to give more phenoxyl radical **39** than phenoxyl radical **40** (Scheme 6).

In the same fashion as the biosynthesis (Section 3.1, Scheme 1), both radicals attack the double bond of the phenylpropene at C-8, eventually resulting in a mixture of 3-aryl- and 2-aryl-1,4-benzodioxanes. As more of phenoxyl radical **39** would have been produced when using silver salts, this favours the formation of a 3-aryl-1,4-benzodioxane, as was observed.

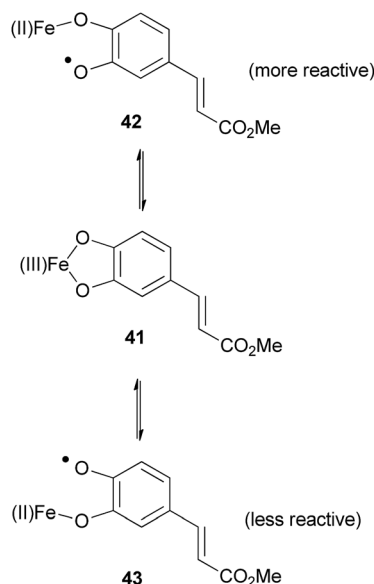


Fig. 7 Two regioisomeric radicals formed using iron salts.²

It is well established that Fe(III) salts form strong complexes with catechols.⁷³ Sefkow suggests that an Fe(III) complex **41** is an intermediate in the coupling reaction (Fig. 7).

The similar oxidation potential of Fe(II)/Fe(III) and of O[•]/O^{•-} in catechols means the two radicals **42** and **43** can equilibrate *via* complex **41**. Radical **42** is less stabilised and therefore more reactive than radical **43**, therefore it primarily couples with the phenylpropene (*e.g.* **7**), favouring the formation of 2-aryl-1,4-benzodioxanes, for example (±)-34.

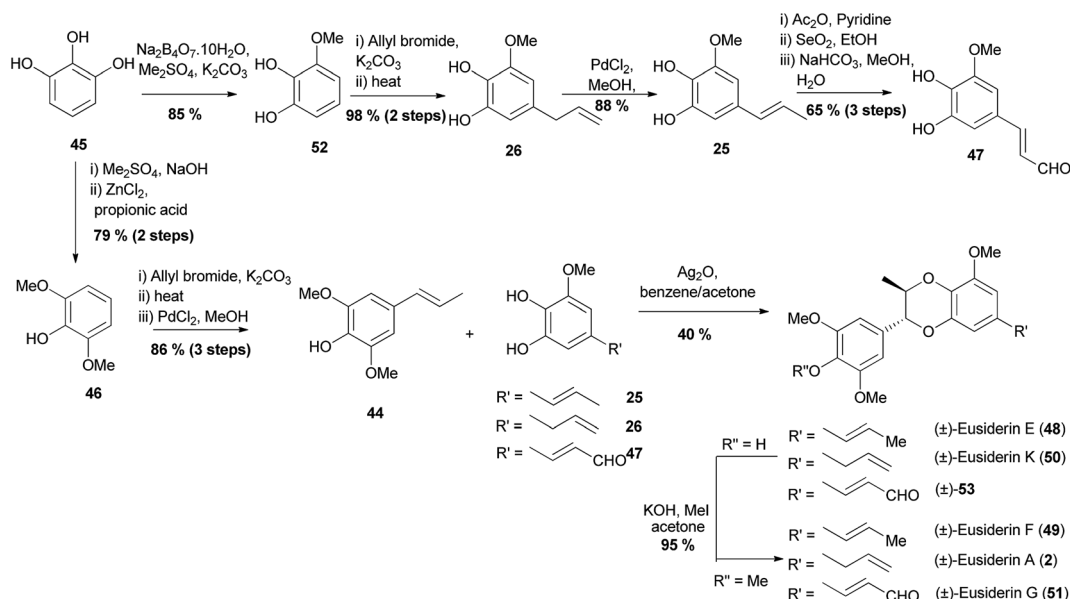
The high selectivity of iron and silver salts has been further exploited by the same group in the synthesis of (±)-sinaiticin **22** and (±)-aiphanol **12**.^{74,75}

4 Synthetic methods to 1,4-benzodioxane oxyneolignans

4.1 Biomimetic approaches and oxidative dimerization

Indisputably the most well-researched route to synthesise 1,4-benzodioxane lignans is the biomimetic synthesis involving





Scheme 7 Synthesis of five members of the eusiderin family by Jing *et al.*^{76,77}

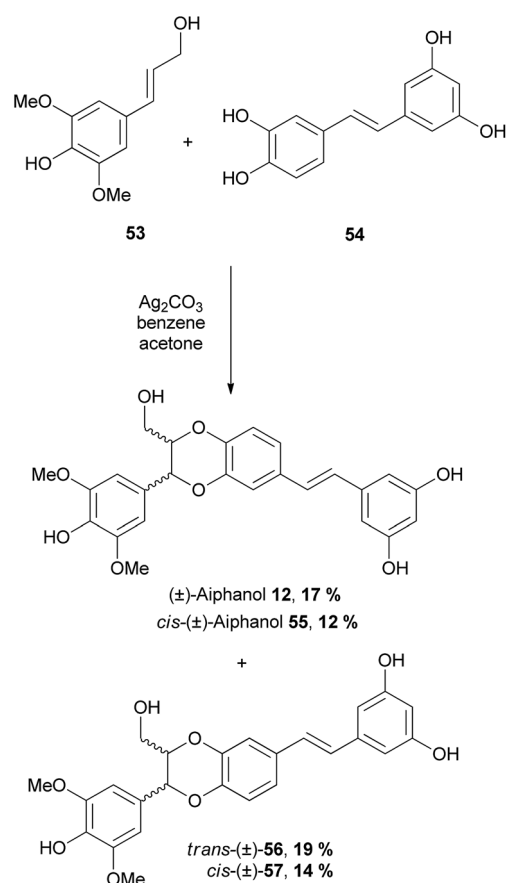
the oxidative dimerisation of phenoxy units to give racemic products (introduced in Sections 3.2 and 3.3).

Subsequent efforts by Jing and co-workers have expanded on the preliminary report by Merlini and Zanarotti, with several members of the eusiderin family synthesised by changing the C_6C_3 units involved in the oxidative coupling using silver oxide in benzene (Scheme 7).^{76,77}

All the eusiderins that were synthesised were done so using phenylpropene 44 as a coupling partner. Phenylpropene 44 was prepared by global methylation of pyrogallol 45, followed by regioselective demethylation to give phenol 46. Allylation of 46 followed by a high-yielding Claisen rearrangement afforded an alkene that underwent PdCl_2 -catalysed migration of the double bond to form phenylpropene 44. Three different *o*-diphenol fragments: 25, 26 and 47, were then prepared to account for the different sidechains on eusiderins E (48) and F (49) compared to K (50) and A (2) and also G (51). The synthesis of these phenylpropene fragments also began with pyrogallol 45 which was selectively methylated to give 52 followed by allylation to give a substrate that underwent a Claisen rearrangement to give diphenol 26. Double-bond transposition gave phenol 25, the allyl group of which was then oxidised to give 47. Oxidative cross-coupling between phenylpropene 44 and either diphenol 25, 26, or 47 was mediated by Ag_2O to give (\pm)-eusiderin E (48), (\pm)-eusiderin K (50) and (\pm)-53 respectively; all with the desired *trans* isomers as major products and in moderate yields circa 40%. Methylation of the 1,4-benzodioxane products with iodomethane gave pure *trans* isomers of (\pm)-eusiderin F (49), (\pm)-eusiderin A (2) and (\pm)-eusiderin G (51).

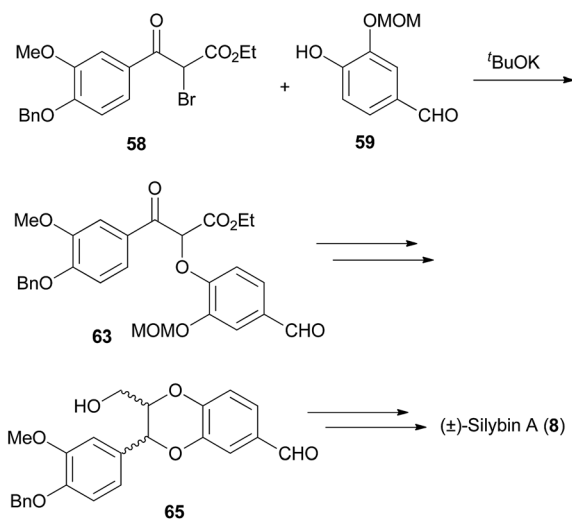
Chand and Banwell⁷⁸ in their biomimetic synthesis of (\pm)-aiphanol 12, used slightly different starting materials in their oxidative coupling – instead of a phenylpropene, they coupled piceatannol 54 with sinapyl alcohol 53, which resulted in (\pm)-aiphanol 12. Three aiphanol isomers; *cis*-(\pm)-55, *trans*-(\pm)-56 and *cis*-(\pm)-57 were also procured directly from the coupling reaction (Scheme 8). The products were separated using semi-preparative HPLC.

(\pm)-56 and *cis*-(\pm)-57 were also procured directly from the coupling reaction (Scheme 8). The products were separated using semi-preparative HPLC.



Scheme 8 Synthesis of (\pm)-aiphanol 12 by Chand and Banwell.⁷⁸



Scheme 9 Synthesis of (±)-silybin A (8).⁷⁹

This method only produces racemic products, and while some 1,4-benzodioxanes are found as racemic mixtures in nature, non-racemic compounds make up a significant portion of isolated natural products. Although a certain degree of regioselectivity is achieved through altering conditions and starting materials, most of these reactions do give both regioisomers and many possible coupling products often isolated. In addition, the respective components of the oxidative dimerisation have to be assembled separately and then combined in the last or penultimate steps of the synthesis.

4.2 Phenolate substitution of a bromine in an α -bromophenone

An effective technique to form a 1,4-benzodioxane hinges on the condensation of an α -bromophenone (e.g. **58**) and a phenol (e.g. **59**) as the pivotal synthetic step (Scheme 9).

This approach was first reported in relation to synthesis of the 1,4-benzodioxane fragment of silybin A (**8**),^{6,7,79} followed by

other compounds including insecticidal sesquignans (e.g. haedoxan A (**19**),²⁷ Scheme 10).^{80–82} The phenolic component requires a second hydroxyl group, that can be protected or unprotected, *ortho* to the phenol substituent, for formation of the 1,4-benzodioxane later in the synthesis.

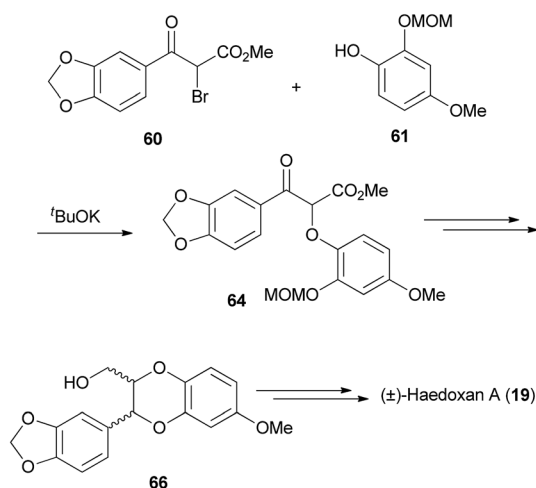
In this approach, the crucial step involved the reaction of racemic 2-bromo-3-oxypropionates **58** and **60** with phenols **59** and **61** to give keto-esters **63** and **64**. Reduction of the ketone, followed by manipulation of protecting groups and acid-catalysed cyclisation gave the 1,4-benzodioxane structures (±)-**65** and (±)-**66**. In all the acidic cyclisation conditions attempted, 1,4-benzodioxane (±)-**66** was isolated as a mixture of *trans* and *cis* isomers.⁶ However, with the slightly different substrate, Tanaka *et al.* obtained only the *trans*-1,4-benzodioxane (±)-**65** using similar conditions to those previously reported.⁷⁹

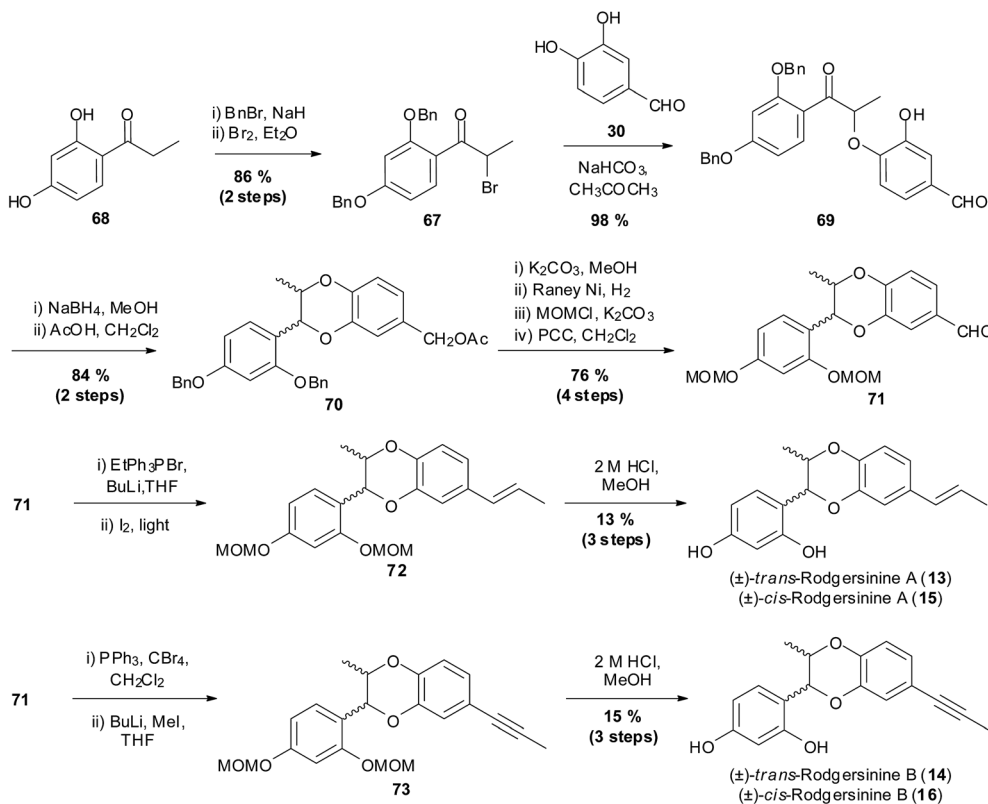
While 2-bromo-3-oxypropionates are required for the synthesis of 1,4-benzodioxanes with a 9-hydroxymethyl (i.e. isoamericanin-type), α -bromopropiophenones (e.g. **67**) are required for the synthesis of 1,4-benzodioxanes with a methyl group (i.e. eusiderin-type). This route has been applied to the synthesis of members of the eusiderin and rogersinine families.^{83–85}

Miao and coworkers reported the racemic synthesis of members of the rogersinine family using this method (Scheme 11).

This synthesis began with 2,4-dihydroxypropiophenone **68** which was benzyl-protected followed by a bromination step to give α -bromopropiophenone **67**. The bromine in α -bromopropiophenone **67** was then displaced by the phenoxide of 3,4-dihydroxybenzaldehyde **30**, to give ether **69**. Global reduction using NaBH₄, followed by acetic acid-mediated cyclisation gave 1,4-benzodioxane **70** in a 2 : 1 ratio of *trans* to *cis* isomers with concomitant acetylation of the benzylic alcohol. The *cis/trans* mixture of isomers was not separated and the remaining synthesis was performed using a *cis/trans* mixture. Next was the conversion of the benzylic ester to an alcohol and a series of deprotection/reprotection steps followed by oxidation with PCC resulted in aldehyde **71**. To synthesise (±)-*trans*-rogersinine A (**13**) and (±)-*cis*-rogersinine A (**15**), aldehyde **71** underwent a Wittig reaction, to give a mixture of *E* and *Z* isomers which were isomerised to give exclusively the *E* isomer **72**, which was then deprotected to give the natural products (±)-**13** and (±)-**15** in 11 steps with an overall yield of 7.1%. To introduce the alkyne functionality, aldehyde **71** underwent a Corey–Fuchs reaction. Subsequent deprotection of the MOM groups of **73** yielded (±)-*trans*-rogersinine B (**14**) and (±)-*cis*-rogersinine B (**16**) in 11 steps with an overall yield of 8.2%.

The main advantage of this method over the oxidative dimerisation method (Section 4.1), is control over which regioisomer (2-aryl or 3-aryl) is produced in the synthesis, rather than a mixture as was seen for the other method. However, like the preceding coupling method, this approach is both racemic and as stated above does not easily allow for the synthesis of a wide range of analogues and similar final products. As shown above in the synthesis of members of the rogersinine family, the sidechain can be manipulated given that there is an appropriate substituent. The substitution on the non-

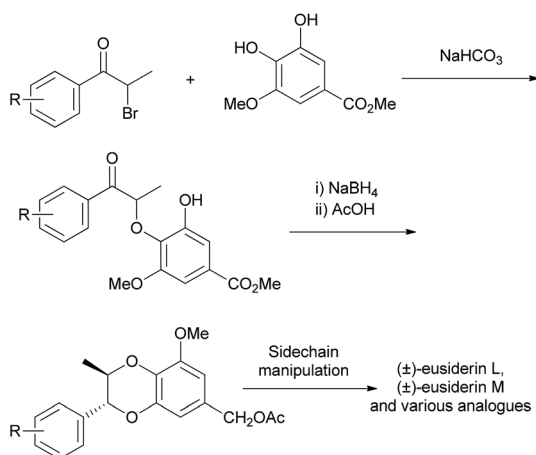
Scheme 10 Synthesis of (±)-haedoxan A (**19**).⁸¹

Scheme 11 Synthesis of members of the rogersinine family by Miao *et al.*⁸³

1,4-benzodioxane aromatic ring, however, cannot be easily changed in the synthesis. When some members of the eusiderin family were synthesised using this approach, different α -bromopropiophenones were prepared and a parallel reaction sequence was required for the formation of analogous 1,4-benzodioxanes (Scheme 12).

4.3 Condensation of an epoxide precursor

The first enantioselective synthesis of a 1,4-benzodioxane was that of a model 1,4-benzodioxane by Arnoldi *et al.* (Scheme 13).⁵⁹

Scheme 12 Synthesis of members of the eusiderin family and analogues.^{84,85}

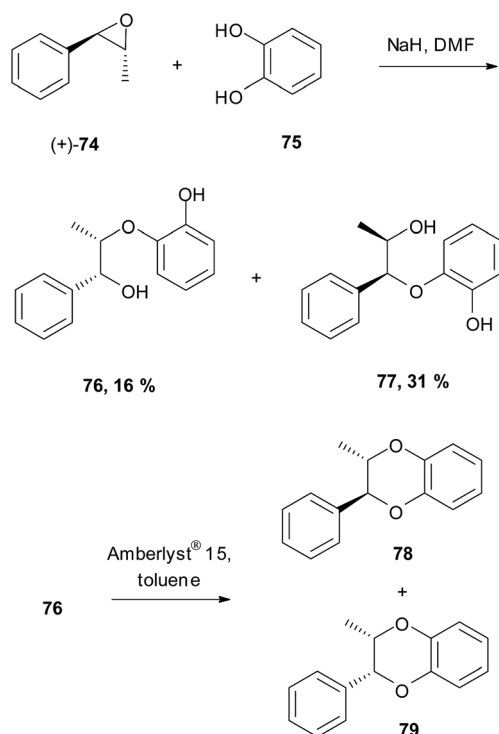
They used the enantiomerically pure (+)-epoxide **74**, derived from ephedrine. Firstly, (+)-**74** was heated at reflux with catechol **75** and NaH in DMF, giving separable diols **76** and **77** in a 1 : 2 ratio. Diol **76** was then cyclised with Amberlyst® 15 in toluene to give *trans*-benzodioxane **78** and *cis*-benzodioxane **79** in a 3 : 2 ratio.

This pioneering work highlighted epoxides as an attractive option for the synthesis of 1,4-benzodioxanes, and even though the asymmetric version has not been applied to the synthesis of any eusiderin-type natural products, it has since been further developed by several groups to synthesise isoamericanin-type natural products.

The first synthesis of 1,4-benzodioxane natural products using epoxides was in 1987 by Tanaka *et al.* (Scheme 14).⁸⁶ The method was carried out using achiral epoxide **80**, and as such gave racemic products. Nevertheless, it provided a novel way to synthesise this type of naturally occurring compound.

The synthesis by Tanaka *et al.* began from caffeic acid **31**, which was esterified, MOM protected and then reduced, to give allylic alcohol **81**. Alkene **81** then underwent epoxidation with *tert*-butyl hydroperoxide (TBHP) in the presence of vanadyl acetylacetonate to give epoxide **80**. Condensation of **80** with either phenol **82**, or its regioisomer **83**, in the presence of sodium hydroxide afforded the respective diols **84** and **85** as the *erythro* products. Mesylation of the primary alcohol in **84** and **85** followed by treatment with base, gave epoxides **86** and **87**, respectively. Removal of the benzyl protecting groups, followed by cyclisation in basic conditions gave *trans*-1,4-benzodioxanes (±)-**88** and (±)-**89**. Horner–Wadsworth–Emmons of aldehydes





Scheme 13 First enantioselective synthesis of a 1,4-benzodioxane structure.⁵⁹

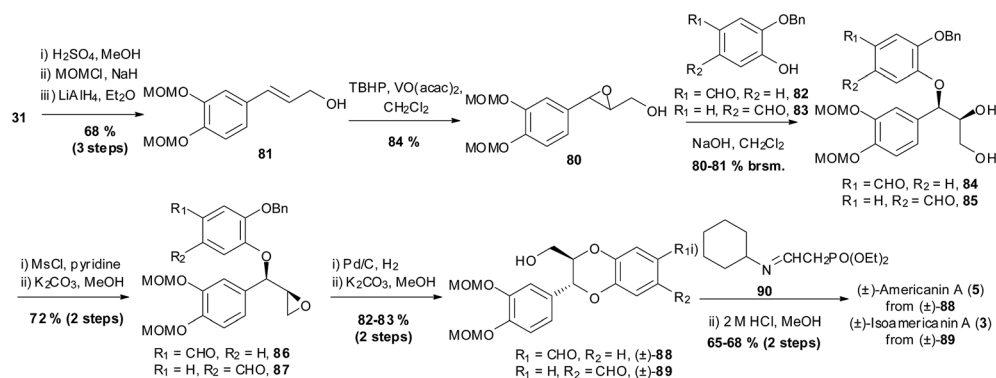
(\pm)-**88** and (\pm)-**89** with phosphonate **90** followed by treatment with acid afforded the natural products (\pm)-americanin A (**5**) and (\pm)-isoamericanin A (**3**).

Gu *et al.* were able to adapt this method, which previously gave racemic products, to an enantioselective synthesis through an asymmetric dihydroxylation and were able to use this to synthesise the 1,4-benzodioxane fragment of silybin A (**8**) (Scheme 15).^{87,88}

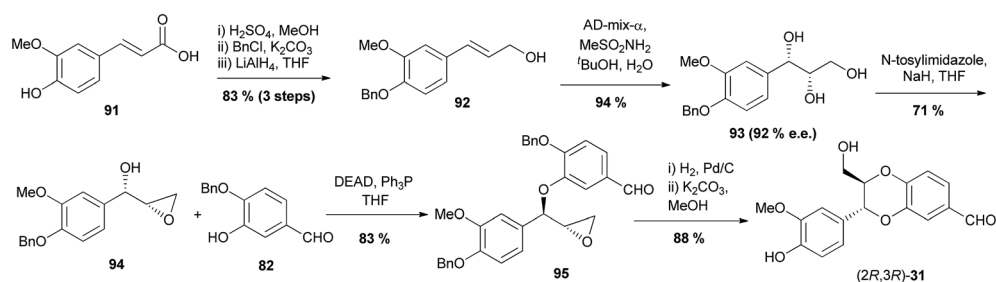
Starting from ferulic acid **91**, a series of esterification, benzyl protection and reduction steps yielded cinnamyl alcohol **92**. This underwent a Sharpless asymmetric dihydroxylation to give triol **93** with a 92% ee. Triol **93** was then converted to epoxyalcohol **94** which then underwent a Mitsunobu reaction with phenol **82** to yield benzyl aryl ether **95**. Removal of the benzyl protecting groups followed by base-mediated cyclisation of the resultant diol produced 1,4-benzodioxane carbaldehyde (2*R*,3*R*)-**31** as the *trans* isomer. Using AD-mix- β as opposed to AD-mix- α in the asymmetric dihydroxylation step provided triol *ent*-**93**, which was then transformed into the enantiomer of **31**.

This method was applied to the synthesis of isoamericanin A (**3**) and isoamericanol A (**17**) by the same group.⁸⁹ Banwell and co-workers also used this method to prepare (–)-aiphanol **12** and (+)-aiphanol **12** using AD-mix- β and AD-mix- α , respectively.³¹

The route was abridged by Ganesh *et al.*⁹⁰ in their racemic synthesis involving the base mediated one-pot condensation-cyclisation step between bromoepoxide **96** and catechol **30** to give model (\pm)-*trans*-1,4-benzodioxane **97** (Scheme 16). The stereochemistry of benzodioxane **97** in this reaction is the result of initial attack of the more reactive 3-phenolate, over the resonance-stabilised 4-phenolate, to the benzylic bromide. Subsequent ring-opening of the epoxide results in the *trans*-1,4-benzodioxane.

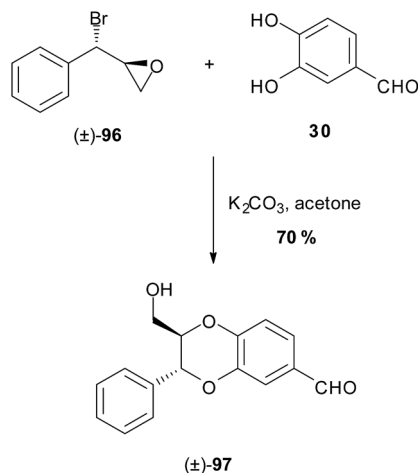


Scheme 14 Synthesis of (\pm)-isoamericanin A (**3**) and (\pm)-americanin A (**5**) by Tanaka *et al.*⁸⁶



Scheme 15 Enantioselective synthesis of the 1,4-benzodioxane fragment of silybin A (**8**).^{87,88}



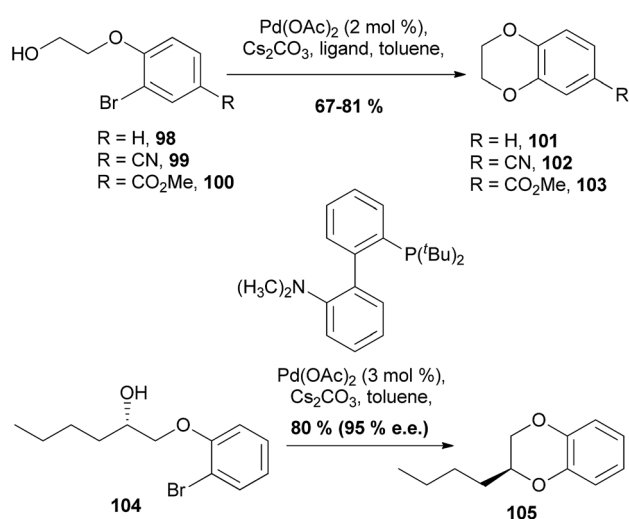


Scheme 16 One pot cyclisation of the model 1,4-benzodioxane (±)-97 by Ganesh *et al.*⁹⁰

This overall synthetic approach offered the first successful asymmetric synthesis of a 1,4-benzodioxane. Depending on the epoxide, the method can produce either racemic or enantio-enriched products. Unfortunately, the asymmetric version has only been applicable to isoamericanin-type 1,4-benzodioxanes and not eusiderin-type. This method also offers regioselectivity of final products, best demonstrated by the separate synthesis of (±)-isoamericanin A (3) and (±)-americanin A (5) by Tanaka *et al.* (Scheme 14). Once again, synthesis of similar compounds using this method is not trivial, especially with compounds that differ in their substitution on the non-1,4-benzodioxane aromatic ring.

4.4 Transition metal assisted methods

In conjunction with the rise in popularity of transition-metal based chemistry in recent years, strategies to synthesise

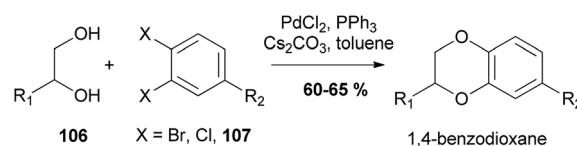


Scheme 17 Intramolecular palladium-catalysed etherification of aryl halides.⁹¹

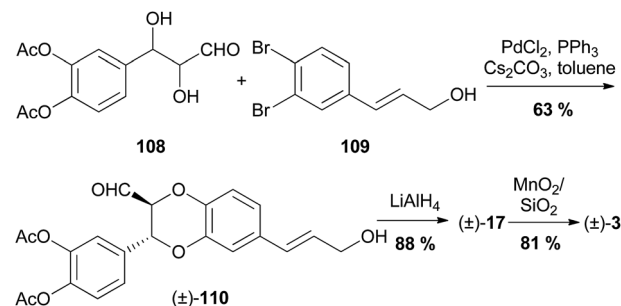
1,4-benzodioxanes using transition-metals have been developed and expanded upon.

4.4.1 Palladium-catalysed etherification of aryl halides.

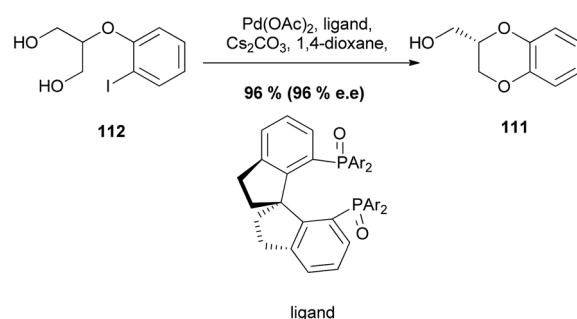
Buchwald and co-workers first reported the formation of 1,4-benzodioxanes using the palladium-catalysed intramolecular



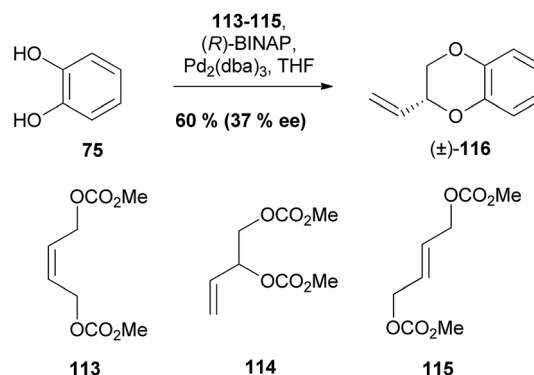
Scheme 18 Coupling of diols 106 and o-dihaloaryls 107 to give 1,4-benzodioxanes.⁹²



Scheme 19 Synthesis of (±)-isoamericanin A (17) and (±)-isoamericanin A (3) by Jing *et al.*⁹²



Scheme 20 Asymmetric synthesis of 1,4-benzodioxane 111 from 112.



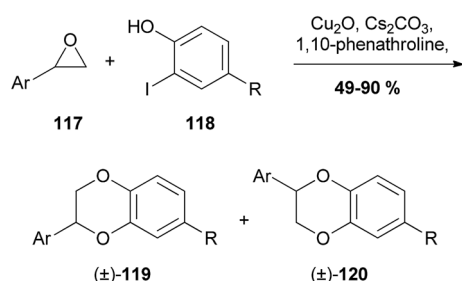
Scheme 21 Palladium-catalysed coupling of catechol 75 with allylic biscarbonates.⁹⁵



etherification of an aryl halide bearing an *ortho* oxyethanol group (Scheme 17).⁹¹

It was found that the reactions with bromides **98–100** in toluene with Pd(OAc)₂ and Cs₂CO₃ successfully gave 1,4-benzodioxanes **101–103**, although the reactions were highly ligand dependent. Cyclisation of optically active alcohols, such as **104** is also possible with the enantiopurity of product **105** being achieved in 95% ee and a yield of 80%.

The reaction can also be performed intermolecularly by coupling a diol (*e.g.* **106**) and a *o*-dihaloaryl (*e.g.* **107**) species (Scheme 18).⁹²



Scheme 22 Copper-catalysed synthesis of 1,4-benzodioxanes by Bao *et al.*⁹⁶

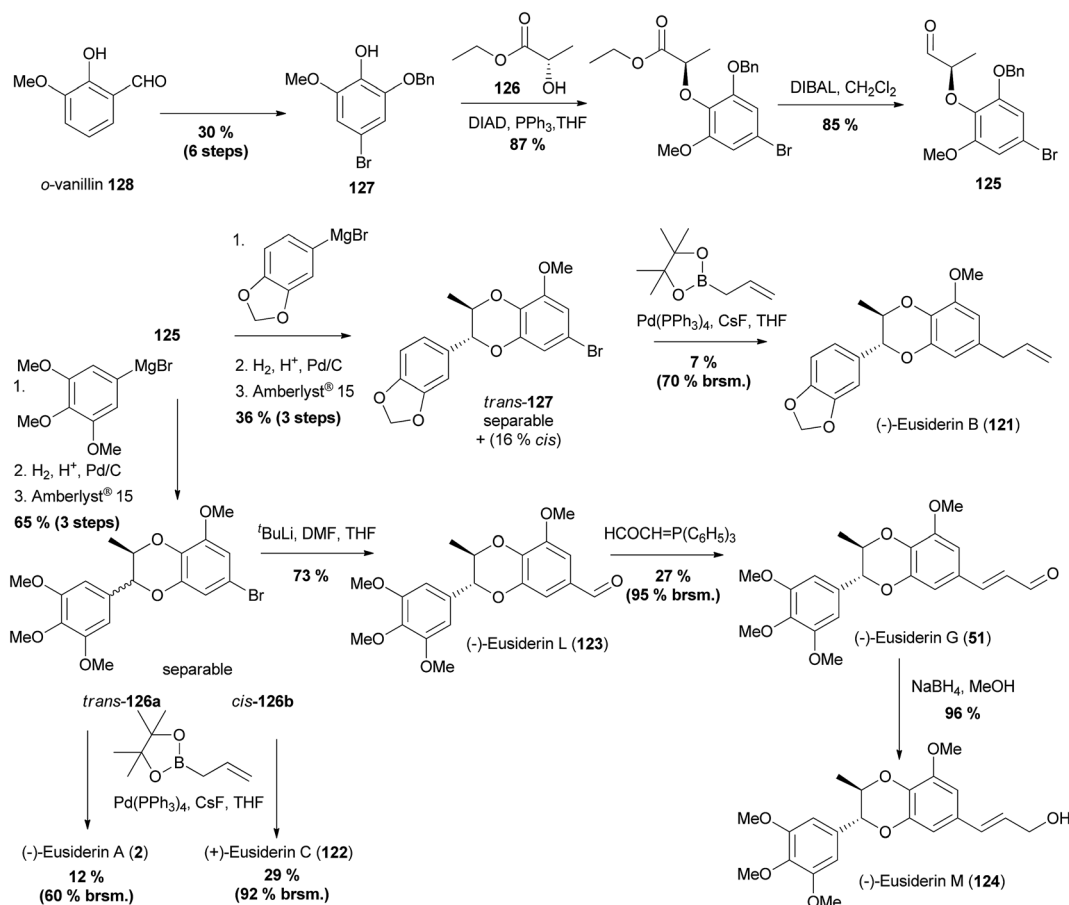
It was found that the reaction did not proceed readily without addition of PPh₃, however when a catalytic amount was introduced, the yield was greatly improved. Following these model reactions, the concept was applied to the synthesis of (±)-isoamericanin A (**3**) and (±)-isoamericanol A (**17**) (Scheme 19).

Diol **108** was coupled with dibromide **109**, using the optimised conditions to give (±)-**110**. Reduction of the aldehyde and removal of the acetyl protecting groups with LiAlH₄ gave (±)-isoamericanol A (**17**) which was oxidised to (±)-isoamericanin A (**3**). Unfortunately, the regioselectivity or *trans/cis* isomerism of the coupled product was not reported.

Recently, the coupling of a chiral dibromide and a catechol was carried out by Rouf *et al.* to give an enantiopure 1,4-benzodioxane which was ultimately converted to (*R*)-doxazosin, an antidepressant drug.⁹³

An enantioselective variant of this reaction has also been reported, forming an asymmetric 1,4-benzodioxane product **111** with 96% ee. In this case, the intramolecular desymmetrization of the 1,3-diol unit in **112** in the presence of a chiral ligand gave the desired chiral product **111** (Scheme 20).⁹⁴

4.4.2 Palladium-catalysed coupling of allylic biscarbonates with diols. Catechol **75** has also been shown to undergo palladium-catalysed coupling with allylic biscarbonates to give enantioenriched 1,4-benzodioxanes (Scheme 21).⁹⁵



Scheme 23 Synthesis of six eusiderin natural products.⁹⁷



Interestingly all of the allyl biscarbonates **113–115** that were trialled gave 1,4-benzodioxane (\pm)-**116** in a 60% yield and an ee of 37%, when ligand (*R*)-BINAP was used, this implies all three starting materials **113–115** form a common intermediate en route to benzodioxane **116**.

4.4.3 Copper-catalysed ring-opening/coupling cyclisation.

Bao and co-workers were able to develop a procedure involving a one-pot reaction between epoxides (e.g. **117**) and *o*-iodophenols

(e.g. **118**), catalysed by a Cu₂O/1,10-phenanthroline/Cs₂CO₃ system (Scheme 22).⁹⁶

It was found that the 3-aryl-1,4-benzodioxane (\pm)-**119** was formed preferentially over its 2-aryl regioisomer (\pm)-**120**. Unfortunately, only terminal epoxides were reacted, and therefore there were no 1,4-benzodioxanes with the potential for *trans/cis* isomers produced and the selectivity cannot be commented on.

While these new approaches to 1,4-benzodioxanes are interesting alternatives to earlier methods, their processes do not address many of the drawbacks of the existing methods. Once again, in all the discussed reactions, the same issue with flexibility is left unchallenged – as with the oxidative dimerisation method, components are assembled first and the 1,4-benzodioxane formed subsequently. Also, with the exception of the example described in the palladium catalysed etherification of aryl halides, all syntheses were racemic and have not been applied to the synthesis of natural products.

4.5 Mitsunobu coupling of phenols and chiral alcohols

A number of 1,4-benzodioxane oxyneolignans have been reported where the pivotal step was the Mitsunobu coupling of a phenol with a chiral alcohol.

This approach was used for the first asymmetric synthesis of six members of the eusiderin family; eusiderins A (**2**), B (**121**), C (**122**), G (**51**), L (**123**) and M (**124**), as well as various analogues.⁹⁷ This was achieved using a divergent synthesis, all from the same chiral aldehyde **125**, derived from the Mitsunobu coupling of (*S*)-ethyl lactate **126** and phenol **127**, itself synthesised from *o*-vanillin **128** (Scheme 23).

Following the synthesis of aldehyde **125**, addition of the appropriate aryl Grignard reagents, deprotection of the benzyl ether and cyclisation yielded separable *trans/cis* mixtures of the cyclised bromides **126a**, **126b** and **127**. Installation of side-chains through either Suzuki cross-coupling reactions (to give **2**, **121** and **122**), or installation of the formyl group in **123** and subsequent manipulation (to give **51** and **124**) provided the final products in a highly efficient synthesis. A subsequent ECD (Electronic Circular Dichroism) study confirmed the absolute stereochemistry of eusiderins A (**2**) and C (**122**) from different

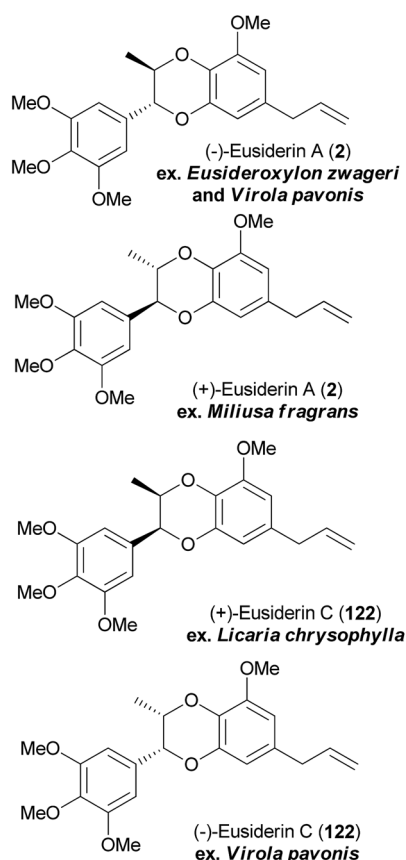
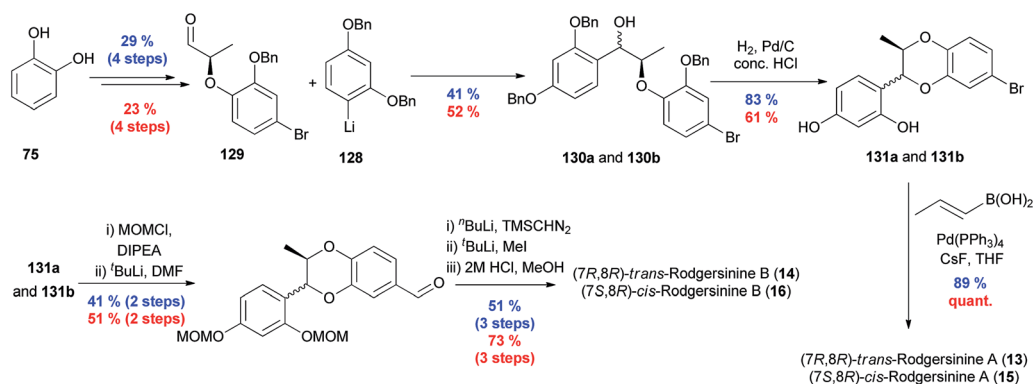
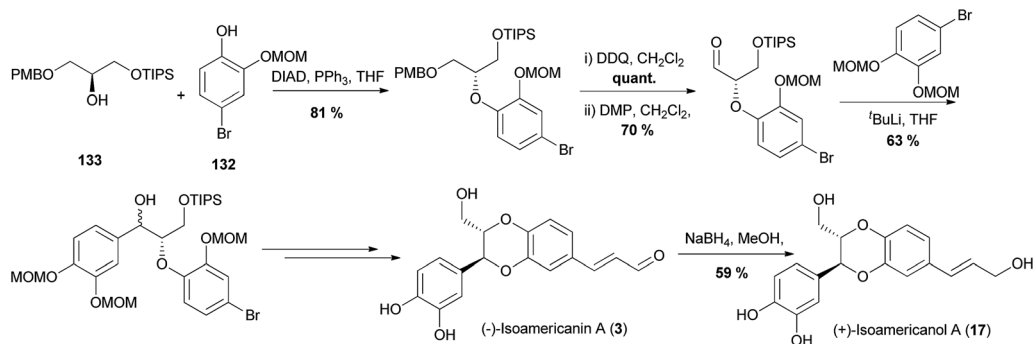


Fig. 8 Absolute stereochemistry of eusiderin A (**2**) and eusiderin C (**122**) from different natural sources.



Scheme 24 Asymmetric total synthesis of *trans*- and *cis*-rodgersinine A (**13**) and (**15**) and B (**14**) and (**16**).²¹ The upper blue percentages are the yields for the shown compounds and while the corresponding enantiomers are not drawn, their yields are indicated as the lower red percentages.





Scheme 25 Mitsunobu coupling of chiral alcohol **133** and phenol **132** *en route* to the synthesis of 2-hydroxymethyl oxynolignans (-)-isoamericanin A (**3**) and (+)-isoamericanol A (**17**).⁹⁸

plant sources (Fig. 8). There was insufficient chiroptical data reported in the original isolation papers to confirm the stereochemistry of the remaining natural products.

This approach was recently applied to the asymmetric synthesis of members of the rogersinine family of 1,4-benzodioxane oxynolignans.²¹ Rather than the aryl-Grignard reagents used in the synthesis of the eusiderin family, this synthesis relied on the addition of the aryl lithiate **128** to aldehyde **129**, providing ethers **130a** and **130b**. This mixture of diastereomers underwent hydrogenolysis and concomitant cyclisation in the acidic conditions, to give a *trans/cis* mixture of 1,4-benzodioxanes **131a** and **131b**, which were then converted to the natural products through installation and side-chain manipulation. This asymmetric synthesis was used to correct the stereochemical assignment of the natural products (Scheme 24).

This route has also been applied to the synthesis of 2-hydroxymethyl-1,4-benzodioxane oxynolignans through the synthesis of members of the isoamericanin family, isoamericanin A (**3**) and isoamericanol A (**17**).⁹⁸ Instead of using a lactate in the Mitsunobu coupling with a phenol (in this case **132**), a glycerol derivative **133** was used to afford the 2-hydroxymethyl structural feature found in the final products (Scheme 25).

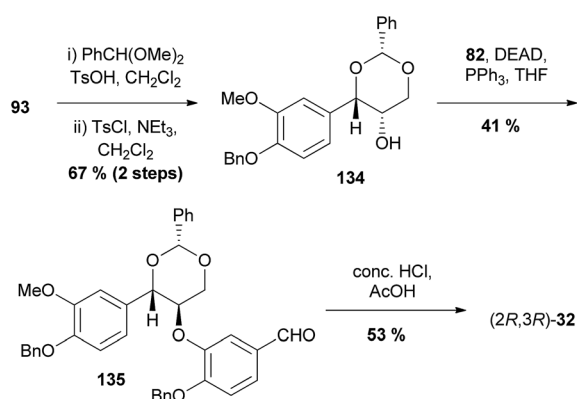
These methods offer a flexible approach to the synthesis of 1,4-benzodioxanes, particularly as both aryl groups are easily modified. The separate aryl units are added sequentially to a

three carbon unit (either lactate or glycerol derived) which accounts for the remaining atoms of the 1,4-benzodioxane.

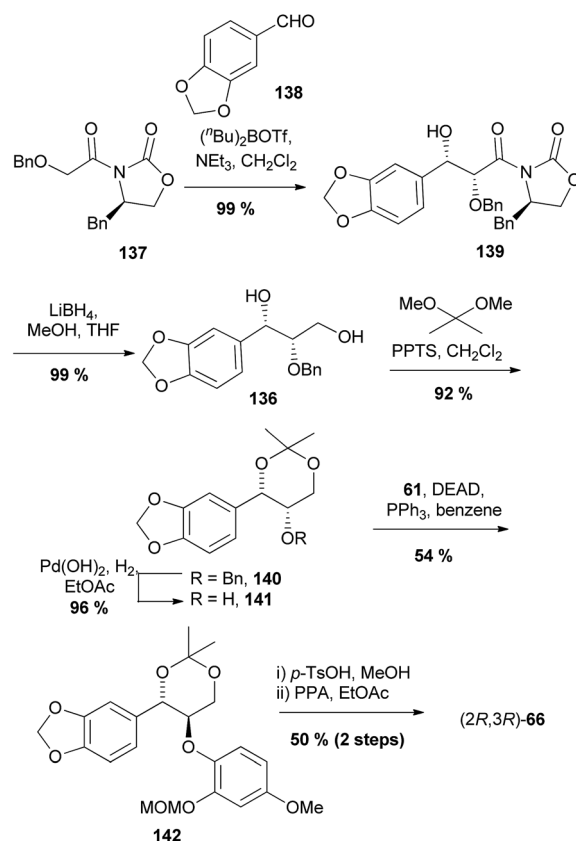
4.6 Alternative syntheses of the 1,4-benzodioxane structure

In addition to the general routes presented above, there are other ways in which 1,4-benzodioxane oxynolignans, or analogues, have been synthesised.

4.6.1 Protection of an asymmetric diol (alternative to the formation of an asymmetric epoxide). In a similar strategy to the epoxide route described previously (Section 4.3), the



Scheme 26 Asymmetric synthesis of americanin-type 1,4-benzodioxane (2R,3R)-**32** by Chen *et al.*⁹⁹



Scheme 27 Asymmetric synthesis of 1,4-benzodioxane (2R,3R)-**66** by Nakamura *et al.*¹⁰⁰



enantiopure triol **93** was the starting material in the synthesis of the americanin-type 1,4-benzodioxane (2*R*,3*R*)-**32** by Chen *et al.* (Scheme 26).⁹⁹

Instead of converting triol **93** (see Section 4.3, Scheme 15) to the corresponding epoxide, benzaldehyde dimethylacetal was used to protect the 1,3-diol to yield benzylidene **134**. A Mitsunobu reaction added the next fragment, phenol **82**, to give **135** and the cyclisation was effected by acid-mediated deprotection of acetal and benzyl protecting groups to give 1,4-benzodioxane (2*R*,3*R*)-**32**.

The same concept was also used in the 1,4-benzodioxane component of haedoxan A (**19**), albeit using an acetone group as an alternative to a benzylidene (Scheme 27).¹⁰⁰

Instead of an asymmetric dihydroxylation to install the stereochemistry of alcohol **136**, an Evan's aldol condensation was used. Oxazolidinone **137**¹⁰¹ underwent an aldol reaction with benzaldehyde **138** to give *syn* aldol adduct **139** in >98% de. Reduction of the aldol provided diol **136** which underwent protection to give acetone **140**. Hydrogenolysis of the benzyl group with Pearlman's catalyst provided alcohol **141**, which was coupled with phenol **61** under Mitsunobu conditions to give ether **142**. Deprotection and cyclisation steps produced (2*R*,3*R*)-**66**.

This method offers many of the advantages and disadvantages presented by the epoxide-based method. Although only applicable to the synthesis of isoamericanin-type 1,4-benzodioxanes, it does produce chiral products with in-built regioselectivity. While the 1,4-benzodioxane aromatic ring is added later in the synthesis and thus can be changed to allow for analogues, the non-benzodioxane aromatic ring is present from

the beginning of the synthesis and as such is not easily altered to provide analogues.

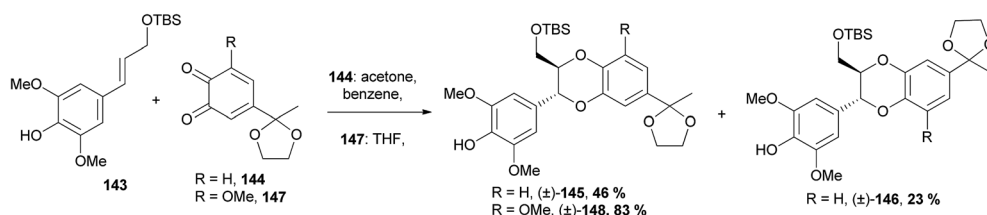
4.6.2 [4 + 2] cycloaddition of a cinnamyl alcohol and *o*-quinone. The [4 + 2] cycloaddition of cinnamyl alcohol **143** and *o*-quinone **144** was achieved by Kuboki and co-workers, to yield 1,4-benzodioxanes (±)-**145** and (±)-**146** (Scheme 28).^{102,103}

It was found that the free phenol and a protected primary alcohol (in this case with TBS) on cinnamyl alcohol **143** were required for a successful cycloaddition. Interestingly, when a methoxy substituent was added to the *o*-quinone, as in **147**, the selectivity of the reaction was greatly increased, with only the isoamericanin-type 3-aryl-1,4-benzodioxane (±)-**148** produced, as opposed to a 2 : 1 mixture of 3-aryl- and 2-aryl-1,4-benzodioxanes (±)-**145** and (±)-**146** as was found when reacting the *o*-quinone **144**.¹⁰³ 1,4-Benzodioxanes (±)-**145** and (±)-**148** were further reacted to procure natural products (±)-aiphanol **12** and (±)-nitidanin, respectively.

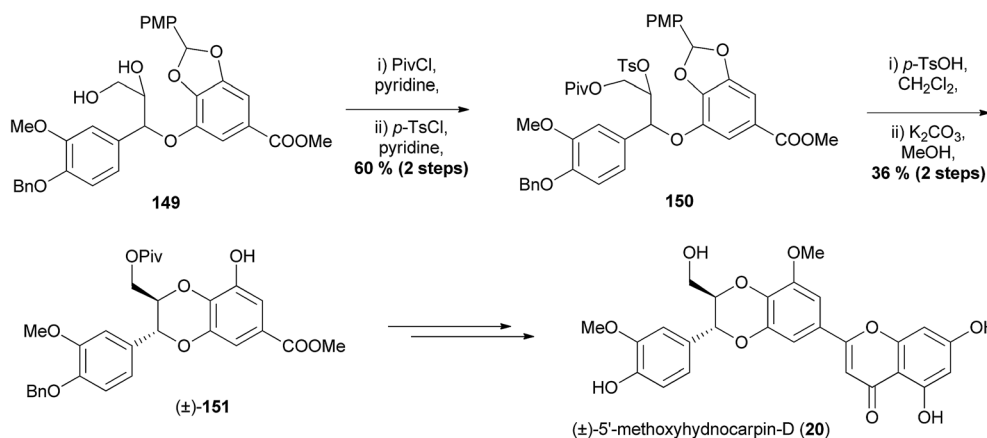
Similar to oxidative dimerisation, this route provides racemic products, and the regioselectivity can be somewhat controlled.

4.6.3 Intramolecular cyclisation of tosylates. In 2001, Valoti *et al.* reported the intramolecular cyclisation of tosylates to give 1,4-benzodioxane structures that were then converted to 2-(aminomethyl)-1,4-benzodioxanes to be tested for their capacity to interact with α_1 -adrenoceptors.¹⁰⁴ This idea was further extended by Chan and coworkers in their synthesis of (±)-5'-methoxyhydnocarpin-D (**20**) (Scheme 29).³⁴

Selective protection of the primary alcohol in diol **149**, followed by tosylation of the secondary alcohol gave ether **150**. The



Scheme 28 Synthesis of 1,4-benzodioxanes (±)-**145**, (±)-**146** and (±)-**148** through a [4 + 2] cycloaddition.^{102,103}



Scheme 29 Synthesis of (±)-5'-methoxyhydnocarpin-D (**20**) by Chan *et al.*³⁴



acetal protecting group was removed by stirring with acid, exposing the phenol for the base-mediated intramolecular nucleophilic substitution to give the *trans* isomer of desired 1,4-benzodioxane (\pm)-**151** which was then converted to (\pm)-5'-methoxyhydnocarpin-**20**.

This example of a racemic synthesis involving the intramolecular cyclisation of tosylates demonstrates another synthesis that can produce isoamericanin-type 1,4-benzodioxanes with regioselectivity. Once again, as is the case with all the aforementioned syntheses, this method is not particularly flexible or able to produce a large number of analogues with variations on both aromatic rings.

5 Summary and conclusions

1,4-Benzodioxane lignans, isolated from a wide range of sources, are a promising sub-class of compounds with a broad range of bioactivities which lend them to be desirable synthetic targets. Their structures are such that a number of synthetic routes, involving a wide range of known and new reactions have been used and developed for their synthesis. A study of the synthesis toward these natural products highlights the evolution in the way that groups approach these targets. Initially, syntheses were mainly racemic with little stereochemical control, but they explored many aspects of these structures, including their formation and characterisation. Regioselective and enantioselective syntheses have since been developed which allowed for the confirmation of natural product stereochemistry. More recently the rise in use of transition-metal chemistry in organic synthesis has translated to the use of these versatile reactions to provide the 1,4-benzodioxane scaffold.

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